FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Pulmonary-Allergy Drugs Advisory Committee

THURSDAY, NOVEMBER 19, 2009

8:00 a.m. to 3:00 p.m.

Washington Hilton/Silver Spring

8727 Colesville Road

Silver Spring, Maryland

Pulmonary-Allergy Drugs Advisory Committee

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I N D E X

P R O C E E D I N G S

8:00 a.m.

DR. BRANTLY: Good morning, ladies and gentlemen. We'd like to begin the meeting now. My name is Mark Brantly. I'm the acting chairman of this particular session.

This meeting is to discuss a supplemental NDA from Boehringer Ingelheim to add a labeling claim for reduction in exacerbations in patients with chronic obstructive pulmonary disease to the labeling of Spiriva HandiHaler.

Discussion will also include recent safety concerns about Spiriva HandiHaler, including

stroke, myocardial infarction, cardiovascular death, and that has been cited in the public domain recently.

I'd like to first begin with the introduction of the committee. We'll start at the far end over there with Curtis.

DR. ROSEBRAUGH: Curt Rosebraugh, Director, Office of Drug Evaluation II.

DR. CHOWDHURY: I'm Badrul Chowdhury, Director, Division of Pulmonary and Allergy Products.

DR. MICHELE: Terri Michele, Medical Officer, Division of Pulmonary and Allergy Products.

DR. IYASU: Solomon Iyasu, Director of Epidemiology, Office of Surveillance and Epi, CDER.

DR. KNOELL: Daren Knoell, Professor of Pharmacy and Internal Medicine at Ohio State University.

DR. PLATTS-MILLS: I'm Tom Platts-Mills. I'm Professor of Medicine at the University of Virginia.

DR. SCHOENFELD: David Schoenfeld, Professor of Medicine at Harvard Medical School and Professor in the Department of Biostatistics at Harvard School of Public Health.

DR. WOLFE: Sid Wolfe, Health Research Group of Public Citizen. I am a consumer representative on the Drug Safety and Risk Management Advisory Committee of FDA.

DR. KHUC: Kristine Khuc, Designated Federal Official.

DR. BRANTLY: Mark Brantly, University of Florida, Professor of Medicine.

DR. NEWMAN: Lee Newman, Professor of Medicine and Professor of Public Health, University of Colorado School of Medicine.

DR. LESAR: Timothy Lesar, Director of Clinical Pharmacy Services, Albany Medical Center, Albany, New York.

DR. TERRY: Peter Terry, Professor of Medicine, Pulmonary and Critical Care Medicine, Johns Hopkins.

MS. HOLKA: Andrea Holka, Patient

Representative.

DR. HENNESSY: Good morning. I'm Sean Hennessy. I do pharmacoepidemiology research at the University of Pennsylvania.

DR. HENDELES: Leslie Hendeles. I'm Professor of Pharmacy and Pediatrics at the University of Florida.

DR. HONSINGER: Richard Honsinger. I practice internal medicine and allergy in Los Alamos, New Mexico and am clinical professor at the University of New Mexico.

DR. BRANTLY: Thank you very much. I'd like to thank the audience for joining us.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look

forward to a productive meeting.

In the sprit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee members take care that their conversations about this topic take place in the open forum of this meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, the FDA will refrain from discussing these details of the meeting with the media until its conclusion.

I would like to remind everyone present to please silence your cell phones and other electronic devices, if you have not already done so. The committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you very much.

Ms. Khuc will read the conflict of interest statement.

DR. KHUC: The Food and Drug Administration is convening today's meeting of the Pulmonary-Allergy Drugs Advisory Committee of the

Center for Drug Evaluation and Research under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208(b)(3), Congress has authorized FDA to grant waivers to special government employees who have potential

financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 208(b)(1), Congress has authorized FDA to grant waivers to regular government employees who have potential conflicts of interest when it is determined that the financial interest is not so substantial to be likely to affect the integrity of the individual's service to the government.

Under Section 712 of the Federal Food, Drug and Cosmetic Act, Congress has authorized FDA to grant waivers to special and regular government employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, members and temporary voting members of the committee who are special and regular government employees have been screened for potential financial conflicts of interest of their

own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

For today's agenda, the committee will discuss and make decisions regarding Supplemental New Drug Application 21-395, Spiriva HandiHaler, tiotropium inhalation powder, for the reduction and exacerbation, worsening of symptoms in patients with chronic obstructive pulmonary disease. This is a particular matter involving specific parties.

Based on the agenda and all the financial interests reported by the members and temporary voting members of the committee, it has been determined that all interests in firms related by the Center for Drug Evaluation and Research present no potential for conflict of interest.

To ensure transparency, we encourage all standing members and temporary voting members to

disclose any public statements that they have made concerning the products at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Richard Hubbard is the industry representative for this committee. However, Dr. Hubbard has been recused from this meeting due to his prior work on Spiriva HandiHaler, the product at issue.

We would like to remind members and temporary voting members of the committee that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

Thank you.

DR. BRANTLY: Thank you, Dr. Khuc.

We'd like to proceed now with the FDA opening remarks, with Dr. Chowdhury.

DR. CHOWDHURY: Good morning. Honorable Chairman, Dr. Brantly, and members of the Advisory

Committee, representatives from Boehringer Ingelheim, and others in the audience, I welcome you at this meeting on behalf of the U.S. Food and Drug Administration.

Dear members of the committee, in this brief presentation, I will introduce the objective of this meeting and questions that we'll discuss and vote upon. We have two objectives for this meeting; first, to discuss Spiriva HandiHaler efficacy claim for the reduction of exacerbations in patients with chronic obstructive pulmonary disease; second, to discuss potential safety issues, which are stroke, myocardial infarction, and cardiovascular mortality, and all cause mortality.

As you hear the presentations, particularly that cover the second objective, you will hear data presented with Spiriva HandiHaler, as well as a different product, called Spiriva Respimat. Both HandiHaler and Respimat deliver the same active moiety, tiotropium bromide, but the devices are different and the drug products are

different. Just keep in mind that these are two different, distinct products and carefully consider whether data generated from one product is applicable to the other or not.

We, the FDA, have a long history and prior precedence where we have not transferred efficacy findings from one product to the other for such locally acting drugs. From an efficacy standpoint, we have considered these products as unique and distinct, each requiring their own set of data to support efficacy claims.

From a safety standpoint, we have been conservative and have applied safety findings generated from one product to other products containing the same active moiety.

I'll now introduce the questions very briefly before I close. There are a total of five questions. Questions 1 and 2 are nonvoting. Questions 3, 4 and 5 are voting. I will show the questions in this and four subsequent slides. I will not read all the questions, because they are available in print at this meeting.

In Question 1, which is shown here on the slide, we are asking you to discuss and comment on mortality data for Spiriva HandiHaler. In Question 2, we are asking you to discuss and comment on mortality data for Spiriva Respimat. Question 3 is on efficacy for COPD exacerbation for Spiriva HandiHaler. This is a voting question.

Question 4 is also a voting question and this is on safety signal of stroke. Question 5 is a voting safety question on cardiovascular safety outcomes.

We look forward to an interesting meeting and I thank you for your time, effort and commitment to this important public health service. Thank you very much.

DR. BRANTLY: Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the Advisory Committee meeting, the FDA believes that it's important to understand the context of individuals' presentations. For this reason, the

FDA encourages all participants, including the sponsor's non-employee presenters, to address the committee about any financial relationship they may have with the firm at issue, such as consulting fees, travel expenses, honorarium and interest in the sponsor, including equity interests and those based on the outcome of this meeting.

Likewise, FDA encourages you, at the beginning of your presentation, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of the presentation, it will not preclude you from speaking.

So let's begin with our sponsors in speaking. Thank you very much.

DR. VOIGT: Good morning, Mr. Chairman, members of the panel, representatives of the FDA. My name is Thor Voigt. I am Senior Vice President-Medicine and Director-Regulatory Affairs with Boehringer Ingelheim.

COPD is a very serious disease; not only

that patients and their families are losing quality of life, COPD patients are suffering, and, unfortunately, many COPD patients are dying prematurely. COPD is the fourth leading cause of death in the United States and there is no cure for this disease.

Boehringer Ingelheim has a longstanding commitment to develop therapies and compounds to help treat COPD patients. Almost 25 years ago, Atrovent inhalation aerosol was introduced in the United States, and in 1996, Combivent inhalation aerosol, and since 2004, we have Spiriva HandiHaler available. I would like to emphasize that specifically for COPD patients, exacerbations play an important role during their daily life and for the disease itself.

Our understanding of the role of Spiriva HandiHaler is informed by a large database which covers, in the meantime, some 17,000 patients from development studies. Furthermore, we have, in the meantime, extensive post-marketing information covering more than 60 million patient years.

For those of you not too familiar with Spiriva HandiHaler, here is a picture of the actual drug product, as well as the current U.S. label indication statement.

Boehringer Ingelheim is seeking approval to obtain a new indication, which is shown here in yellow. Spiriva HandiHaler is indicated to reduce exacerbations in COPD patients.

The focus of today's meeting will be basically on two topics; firstly, Boehringer Ingelheim's proposal for a new label expansion, reduction in COPD exacerbation. This is based on data from two studies; firstly, the Veterans' Affairs exacerbation study, which was a study solely done in the United States in 1,800 patients for six months in a Veterans' Affairs setting; and, secondly, on UPLIFT.

UPLIFT is, to the best of our knowledge, one of the largest, if not the largest study ever done in COPD patients. The study enrolled 6,000 patients. The study had a duration of four years. The study was done worldwide in almost 500 sites.

UPLIFT was designed to test the very challenging hypothesis that the maintenance use of Spiriva HandiHaler could alter the progression of the disease and this is even within the context of permitted use of other respiratory medications, except anticholinergics.

Also, UPLIFT did not meet its primary hypothesis to show reduction in long-term decline of lung function. It provided valuable important and robust data on Spiriva HandiHaler in COPD patients; for example, reductions in exacerbations.

The second topic of today will be the safety of Spiriva. For this, again, we will discuss the data from UPLIFT. We will discuss data from observational studies, as well as data from two large pooled safety analyses.

The first covers 26 Spiriva HandiHaler trials, all placebo controlled, and the second covers five Spiriva Respimat studies. Spiriva Respimat is an alternative formulation which is not available in the United States. It's registered in Europe and some ex-European countries.

We at Boehringer Ingelheim believe that UPLIFT and the VA studies support the new indication, reduction of exacerbations. We, furthermore, believe that we have important and compelling safety information about Spiriva HandiHaler specifically with regard to cardiovascular events, stroke and mortality.

This is an overview of today's presentation. I already very briefly alluded to the role and importance of exacerbations in COPD patients, and in a few sessions, you will hear Professor Tashkin, Professor Emeritus Don Tashkin from UCLA, talking somewhat more in detail about the role and importance of exacerbations for COPD patients.

He will be followed by Dr. Steven Kesten. Dr. Kesten is Vice President-Medicine, Marketed Products-Respiratory at Boehringer Ingelheim. Dr. Kesten will, in depth and detail, describe to you available safety information and efficacy information on Spiriva.

I want to thank the following

consultants, who are with us today, in order to help answer questions you may have. With this, I would like to hand over to Dr. Tashkin.

I would like to thank the following consultants on this list, and I would like to thank you for your time and your attention.

DR. TASHKIN: Good morning. I'm Don Tashkin, Emeritus Professor of Medicine at the David Geffen School of Medicine at UCLA in the Pulmonary and Critical Care Division.

By way of disclosure, I have received grant support and/or financial compensation for consultative services, including serving on advisory boards and for speaking, from Boehringer Ingelheim and Pfizer, as well as from the other pharmaceutical companies listed on this slide.

I'd like to begin with a little discussion, or description really, of my background and experience. COPD has been a major focus of my research for over 30 years. I have been principal investigator of a number of NIH studies related to COPD, including the UCLA population study on

chronic obstructive respiratory disease, which is a study that looked at the relationship between air pollution and the development and progression of airflow obstruction in various census tracts in and around Los Angeles.

I've also been the principal investigator of the various Lung Health Studies. Lung Health Study I was an early intervention study in COPD and it was extended in Lung Health Study III for as long as 14 years.

I currently am principal investigator of the SPIROMICS study. It's an NHLBI initiative to examine biomarkers within distinct phenotypes of COPD to see whether or not they may be predictive of intermediate and long-term outcomes.

I also have served as the principal investigator of the UPLIFT trial and other industry-sponsored clinical trials involving COPD. I think most importantly of all, I've been involved in the care of patients with COPD over the 40-plus-year history of my professional involvement.

In discussing the clinical course of

COPD, which is impacted by periodic exacerbations, I think it -- I'm sorry -- in discussing the importance of exacerbations, I think it's important to consider the clinical course of COPD that's impacted by recurrent exacerbations.

Now, COPD is a chronic progressive disease with underlying inflammation. The inflammation in predisposed individuals leads to structural changes, as well as physiologic abnormalities that are listed here, airflow obstruction, air trapping and hyperinflation, which, in turn, lead to the cardinal symptom of COPD, which is shortness of breath with exertion.

So when patients experience increasing difficulty breathing during physical activity, they naturally reduce their level of activity, leading to physical deconditioning, with structural and functional changes in the skeletal muscle that makes it harder for them to exercise, causing increasing breathlessness, with a vicious cycle that impairs their quality of life. This process is progressive and eventually leads to physical

disability, respiratory failure and death.

Now, the course of COPD is punctuated by recurrent exacerbations. These are acute events that are characterized by an increase in respiratory symptoms, particularly dyspnea, cough and the production of sputum, with sputum purulence on occasion.

Now, these exacerbations then are associated with an increase in the impairment in the mechanics, the mechanical function of the lung, more airflow obstruction, particularly more hyperinflation that actually are responsible for the symptoms.

As the exacerbation recovers, there is a gradual improvement in lung mechanics, along with an improvement in dyspnea. But patients may not return to their baseline level of lung function. Associated with these symptoms is an impairment in quality of life, which is at least temporary, and sometimes the quality of life, which takes a long time to resolve, if it resolves completely at all, does not return to the baseline level of health

status.

There is also evidence that exacerbations, particularly more frequent exacerbations, are responsible for accelerating the progression of the disease, leading to earlier development of disability, respiratory failure and death.

Now, regarding the risk of mortality from exacerbations, there have been a number of studies that have shown a reduced survival in association with exacerbations, with the figures ranging from about 2 and a half percent to 30 percent in the literature. This well conducted longitudinal study in which patients who were hospitalized for an exacerbation of COPD were followed for up to three years.

Eight percent of them died in the hospital. This is consistent with data from other studies. At six months, 24 percent of them were dead; at one year, 33 percent; two years, 39 percent; four years, 49 percent.

Now, this figure compares with about a 33

percent mortality in patients with COPD in general, according to David Mannino's analysis from surveillance data in the U.S. Also, a very recent publication in Respiratory Medicine from a Spanish group showed a 14 percent increased risk of death with each succeeding exacerbation.

This slide illustrates the changes in lung function that occur during recovery from an exacerbation. We see, in the blue line, improvement and gradual improvement in airflow, reflected by the FEV1, and gradual and greater improvement in entry capacity, which is a reflection of the reduction in hyperinflation.

Now, these changes mirror reciprocal changes that occur in the run-up to an exacerbation, which are very difficult to ascertain, because you don't know what patient is going to exacerbate. So it's easier actually to look at the changes that occur during recovery from an exacerbation.

I think that these findings provide a possible rationale that might explain why a drug

like tiotropium may prevent exacerbations or reduce the frequency of exacerbations. Tiotropium does lead to a sustained improvement in FEV1 and sustained improvement or reduction in hyperinflation. And it's very possible and, I think, likely that this effect of tiotropium impacts on the -- that is, mitigates, rather, the impact of any trigger that might insult the lung that might otherwise cause an exacerbation or a worsening of symptoms that would lead the patient to seek additional treatment from his health care provider.

So I'd like to close with some observations and considerations. COPD is a chronic, progressive disease. It is associated with recurrent exacerbations that add to the morbidity and mortality of the disease. Exacerbations are clinically meaningful events. They have short and long-term consequences, worsening of symptoms, lung function, quality of life, at least temporary disability, the need for additional treatment, including hospitalization,

which is the major driver of the cost of COPD, and an increased risk of death.

The totality of evidence, including results from clinical trials, which are mirrored by my own clinical experience and that of my colleagues, has shown that tiotropium is safe and effective in the COPD, including the reduction of the risk for and the rate of exacerbations and hospitalizations related thereto.

Finally, as a clinician, I think it is important to communicate the benefits of tiotropium on exacerbations to patients and their healthcare providers in order to make them aware, or make sure that they are aware, of this important treatment benefit or treatment option in reducing morbidity from COPD.

Thank you very much.

DR. KESTEN: Good morning. My name is Steven Kesten. I am a pulmonary physician and I previously practiced medicine at the University of Toronto and at Rush-Presbyterian St. Luke's Medical Center in Chicago. I'm currently Vice President-

Medicine for Marketed Products in Respiratory for Boehringer Ingelheim.

My task today is to summarize an extensive efficacy and safety program in a focused and concise presentation and in a manner that provides you with the critical information that will allow you to assess the benefits of tiotropium on exacerbations of COPD and respond to the questions posed by the agency today. The data demonstrate that tiotropium reduces exacerbations of COPD and does not increase the risk for cardiovascular events, fatal events, or stroke.

I will begin my presentation with a brief overview of the development program. I will then describe the study design and exacerbation outcomes from the VA study. Next, I will discuss the UPLIFT study, including the study design, FEV1 endpoints, and exacerbation endpoints. I'm also going to show how an analysis of the safety data provides further supportive information for the exacerbation benefits.

Regarding safety, I'm going to be

focusing on fatal events, cardiovascular events and stroke and predominantly rely on the largest single trial that we have with tiotropium, which is the four-year UPLIFT trial with tiotropium HandiHaler.

I will also supplement this information with data from the larger pooled clinical trial database with HandiHaler, as well as bringing in information from the alternative formulation of tiotropium, not available in the United States, that's tiotropium Respimat, and some summary information from observational studies. My conclusions will be based on the totality of the data.

There were approximately 2,600 patients who participated in Phase III trials of six to 12 months duration. For the purposes of the analysis I'm going to show today, I'm restricting that population to those who either received tiotropium HandiHaler or the matching placebo; that is, anyone who received other active drugs, such as ipratropium or salmeterol are excluded.

This leaves 1,723 patients. The

registration trials demonstrated tiotropium's bronchial dilator efficacy over 24 hours with once-daily dosing. Secondary endpoints showed sustained improvements in symptoms and reductions in exacerbations.

It was these secondary endpoints that formed the basis of the much larger Phase III-B and IV clinical trial program, which includes the Veterans' Affairs exacerbation trial involving 1,829 patients, as well as the four-year UPLIFT trial, involving 5,992 patients. The results from the VA study were published in the Annuls of Internal Medicine and the results from the UPLIFT study were published in the New England Journal of Medicine last year.

In addition, there are approximately 7,500 patients who participated in other Phase III-B and IV clinical trials that formed a larger pooled clinical trial database. Now, for inclusion into the safety database, the trials had to be parallel grouped, placebo controlled, and at least four weeks in duration and in the COPD indication.

All together, there are 26 trials, yielding over 17,000 patients. This is all with the HandiHaler formulation and, as I said, there is information from the alternative formulation, Respimat, which I will discuss later in the presentation.

The basis for the request for an indication for a reduction in exacerbation comes from the VA exacerbation trial and the UPLIFT trial. I will begin the discussion of data with the VA study. Again, the Phase III trials showed that tiotropium HandiHaler reduced exacerbations of COPD as a secondary endpoint. We, therefore, sought to design a prospective study specific for exacerbations.

The VA trial was a randomized, double blind, placebo controlled, parallel group trial of six months duration, conducted in 26 VA centers from across the country. As compared to the original Phase III-B and IV -- Phase III clinical trials, the inclusion and exclusion criteria were liberalized. All patients were allowed to take all

respiratory medications, other than inhaled anticholinergics, throughout the trial. So they could use inhaled steroids, long-acting beta agonists, combinations of the two, theophyllines, et cetera.

The co-primary endpoints, which were tested sequentially, were, first, the proportion of patients with at least one exacerbation and, second, the proportion of patients with at least one hospitalization. Of note, we asked that the investigators follow all patients, even those who discontinued drug prematurely, for the exacerbation endpoint for the full duration of the trial.

Secondary endpoints included other exacerbation outcomes, including time to first exacerbation and time to first hospitalized exacerbation. Other secondary endpoints included spirometry comparisons at clinic visits.

As expected in the VA system, the vast majority of the patients were men. The average age was 68 years and the mean FEV1 was 36 percent of predicted normal. Concomitant respiratory

medication use was common, with 38 percent of patients using a long-acting beta agonist and 58 to 61 percent of patients using an inhaled corticosteroid.

We screened approximately 2,500 patients, of which 1,829 were randomized, with roughly equal distribution to both treatment groups. More patients prematurely discontinued study medication in the placebo group compared to the tiotropium group. As I said, we asked at the investigators follow all patients throughout the trial, even those who discontinued study medications, but still more patients in the placebo group prematurely discontinued the study compared to the tiotropium group.

For the first co-primary endpoint, tiotropium reduced the proportion of patients experiencing at least one exacerbation, with a P value of 0.037. Hospitalizations for COPD were experienced by less than 10 percent of the population. Tiotropium was associated with a relative reduction of 26 percent for the proportion

of patients with at least one hospitalized exacerbation, with the P value being 0.056.

A cumulative incidents rate display for an exacerbation is shown in this figure. The probability of an exacerbation is on the vertical axis and time through six months on the horizontal axis. The number of patients at risk by treatment group at each visit are shown at the bottom.

Now, a patient remains at risk until they've had the event of interest, exacerbation, or have been discontinued from the trial for another reason. The green solid line represents tiotropium. The yellow dashed line is placebo. The hazard ratio is an expression of the relative risk of tiotropium to placebo. The hazard ratio of 0.83 indicates a 17 percent reduction in the risk for an exacerbation, the nominal P value being 0.03.

A similar figure is displayed here for the risk of a hospitalized exacerbation, again with the probability of a hospitalized exacerbation on the vertical axis and time through six months on

the horizontal axis. The hazard ratio of 0.72 shows a 28 percent reduction in the risk for a hospitalized exacerbation, with a nominal P value of 0.05.

The number of exacerbations and number of hospitalized exacerbations per patient year while in the study is shown in this table. Other secondary exacerbation endpoints are shown in your briefing document.

The number of events were compared using Poisson regression, adjusted for treatment and center effects and corrected for treatment exposure and over-dispersion. The rate ratio is that of tiotropium to placebo. Tiotropium was associated with a lower rate of exacerbations and a lower rate of hospitalized exacerbations.

Subgroup analyses were performed to examine for the risk of an exacerbation according to various baseline characteristics in order to see if there were some population that were skewing the results. In this figure, I have displayed age, smoking behavior and antibiotics, steroids or

hospitalizations for COPD in the year preceding randomization.

Now, the number of patients by treatment group and subgroup are in your briefing document and have been omitted from this and similar figures simply for ease of viewing. These squares represent the hazard ratios and the horizontal lines are the associated 95 percent confidence intervals.

The yellow vertical line represents unity, with values on the left favoring tiotropium, values on the right favoring placebo. Across these groups, there does not appear to be any subgroup that is predominantly responsible for the results or skewing the results.

Further subgroups are shown here according to concomitant respiratory medication use and baseline FEV1 severity. The medications include long-acting beta agonists, inhaled steroids, the combination of the two, theophylline and anticholinergics. Anticholinergics were the only medications that were discontinued at

randomization.

FEV1 severity is based on the American Thoracic Society criteria, which was used at the time of the study. Again, there's a relatively homogeneous reduction in the risk of an exacerbation, with no particular subgroup that appears to be predominantly responsible for the results.

I'd like to now move on to describe the UPLIFT trial. The Phase III results have led us to hypothesize that tiotropium might alter the rate of decline of FEV1, which is characteristic of the progression of COPD.

We sought to test this and other hypotheses with the UPLIFT trial. UPLIFT is a randomized, double blind, placebo controlled, parallel group trial of four years' duration, involving over 30 countries from around the world. As with the VA study, the inclusion and exclusion criteria were liberalized compared to the Phase III trials. All patients were permitted to use all respiratory medications other than inhaled

anticholinergics.

Now, we specifically sought to have this incorporated into both the VA and UPLIFT trials in order to have trials that would have a real world setting, as much as possible within the confines of controlled clinical trials, in order to have results that would be clinically applicable to the type of patients that you and others may see in the community, despite the challenges it creates in trying to show treatment effects.

The co-primary endpoints were the yearly rate and decline in pre and post-bronchodilator FEV1. Key secondary endpoints that were specified in the statistical analysis plan were time to first exacerbation and time to first hospitalized exacerbation.

Other secondary endpoints include spirometry comparisons at each time point, other COPD exacerbation variables, health-related quality of life as measured by the St. George's Respiratory Questionnaire, and mortality.

Now, regarding mortality, we introduced

two amendments during the trial. The first amendment established the procedure for collecting vital status information from prematurely discontinued patients. By vital status, I'm referring to whether the patient was alive or dead, and if they had died, what was the cause of death and the date of death. The second amendment established the Mortality Adjudication Committee so that there would be an independent judgment of the primary cause of death in a standardized fashion.

We screened over 8,000 patients of which 5,992 were randomized and received medication, 3,006 to placebo, 2,986 to tiotropium. More patients prematurely discontinued study medication in the placebo group. The most common reason was an adverse event, which was also more common in the placebo group.

Approximately three-quarters of the population were men, but this still led to the population including over 1,500 women who were randomized to study medication for up to four years. The average age was 65 years. The mean

baseline pre-bronchodilator FEV1 was about 40 percent of predicted, which improved to approximately 48 percent of predicted following sequentially administered ipratropium-four puffs and albuterol-four puffs. The UPLIFT cohort, therefore, had a population which included approximately 46 percent of patients in Gold Stage 2 or considered as having moderate COPD.

Concomitant respiratory medication use was extremely common in the UPLIFT trial, with 60 percent of patients using a long-acting beta agonist and 62 percent receiving an inhaled corticosteroid.

FEV1 is shown in this figure from 1 to 1.5 liters on the vertical axis and time over 48 months is on the horizontal axis. The values displayed are the estimated means, morning pre-bronchodilator FEV1. Green, again, is tiotropium, yellow is placebo.

As you can see, the slopes of these lines do appear similar and there was no difference in the first co-primary endpoint of rate of decline in

morning pre-bronchodilator FEV1. However, we did see the expected improvements in lung function, reflecting the bronchodilator effects of tiotropium, and these improvements were maintained throughout the trial with no evidence of tolerance, the average changes ranging from 87 to 103 ml. However, as the primary endpoint of rate of decline did not show statistical significance, this and subsequent statistical testing is considered descriptive and P values are nominal.

These two lines represent the estimated mean post-bronchodilator FEV1 as clinic visits. Again, these slopes of the line are similar and there was no difference in the rate of decline in FEV1. But we did see improvements in lung function throughout the trial, with no evidence of tolerance, and this is despite both groups having received eight puffs of short-acting bronchodilators.

I'd like to now move on to the exacerbation findings. The cumulative incidence rate for an exacerbation is shown in this figure,

with the probability of an exacerbation on the vertical axis and time through 48 months on the horizontal axis. The hazard ratio of 0.86 shows a 14 percent reduction in the risk for an exacerbation. The upper limits of the confidence interval are 0.91 and the nominal P value is less than 0.001.

A similar figure is shown here for the probability of a hospitalized exacerbation, with the same hazard ratio, 0.86, showing the 14 percent reduction in the risk of a hospitalized exacerbation. The nominal P value is 0.002.

Now, consider that these exacerbation findings are seen in the setting of substantial use of concomitant respiratory medications, including medications that are known to have an effect on exacerbations.

The number of exacerbations and number of hospitalized exacerbations per patient year while in the study is shown in this figure. Again, the other exacerbation endpoints are included in the briefing document. Tiotropium was associated with

a lower rate of exacerbations. However, the number of hospitalized exacerbations was not different, despite the fact that there was a lower risk for hospitalized exacerbations. It's possible that the decisions and interventions that occur after a first hospitalized exacerbation may have influenced the risk of a subsequent event.

We've looked at subgroup analyses for the risk of an exacerbation according to various baseline characteristics to see if there is a subgroup that might have been predominantly responsible for the results.

In this and the next series of figures, I am showing various subgroups. This figure has age, smoking behavior, and antibiotic, steroids or hospitalizations for COPD in the year preceding randomization. What you see is a generally homogeneous reduction in exacerbation risk across subgroups, with no particular subgroup predominantly responsible.

Further subgroups are shown here according to gender and concomitant respiratory

medication use, long-acting beta agonist, inhaled steroids, the combination of the two, and anticholinergics.

I'd like to note that the finding of exacerbation reductions here with men confirms the results that we've seen in the VA study and highlight that there were over 1,500 women in the UPLIFT trial who were followed for up to four years and the exacerbation findings appear to equally apply to women with COPD in the UPLIFT trial.

Further subgroups are shown according to Gold Stage, moderate, severe and very severe disease, as well as regions across the world. For the United States, there were over 1,500 patients and the findings for exacerbations in the UPLIFT trial, again, are equally applied to residents of the United States.

An analysis was conducted of low respiratory tract events, such as exacerbations, respiratory failure, pneumonia, that were reported as adverse events by investigators during the UPLIFT trial. Now, the purpose of this analysis

was to look for a consistency in the database and perhaps further supportive evidence for the exacerbation outcomes. This analysis has also been repeated for the entire pooled clinical trial safety database, which is included in your briefing document.

Adverse events that are reported in are coded with a standard dictionary to diagnostic terms referred to as preferred terms. These are lumped together into organ classes. So for this example, in the table I'm going to show, it's for all low respiratory tract disorders.

The table displays all adverse events, serious adverse events, and fatal adverse events for low respiratory tract disorders. The N refers to the number of patients with at least one event. IR is the incidence rate per 100 patient years of exposure. The incidence rate is determined by taking the total number of patients with an event and dividing it by the total patient time at risk within a group.

RD is incidence rate difference incidence

rate of tiotropium minus the incidence rate of placebo. Now, we've chosen incidence rate differences for this display and all of the subsequent displays for adverse events that I will be showing as incidence rate differences are able to show either increased or decreased risk, even when there are zero events within a treatment group. As well, this is an approach that has been used in the past by the agency and it also has the advantage of providing the information regarding the number of patients affected per person time.

So looking at the incidence rate for the tiotropium group, it appears that it is lower than the incidence rates in the placebo group, and this is reflected by these negative rate differences. Attached to the rate differences are 95 percent confidence intervals, and this is to show the statistical reliability of the rate difference estimates.

A star is attached wherever the 95 percent confidence interval's upper or lower limits exclude zero, implying a nominal P value of less

than 0.05. So the upper limit of the confidence interval excluded zero for adverse events and serious adverse events on the low respiratory tract disorders.

One of the specific preferred terms under low respiratory tract disorders is respiratory failure and we conducted an analysis of respiratory failure as reported and coded through adverse event reporting.

This table is identical to what I've just shown you; adverse events, all adverse events, serious adverse events and fatal adverse events for the term "respiratory failure." N is the number of patients with an event, IR is the incidence rate, and RD is the rate difference per 100 patient years at risk.

There are over 200 patients with this event. The incidence rates in the tiotropium group are lower than the placebo group, reflected by the negative rate differences. With all three values, the upper limits of the confidence interval exclude zero.

Now, I certainly recognize the limitations of this kind of an approach and there have been no corrections for multiple comparisons. However, consider that the investigators in the UPLIFT trial are predominantly pulmonary physicians or physicians with specific expertise in respiratory medicine and there is no trial-related factor that would cause a preferential reporting of the term "respiratory failure," other than the treatment allocation itself.

Again, the purpose of this analysis is to show the consistency in the database with regard to exacerbation reduction and further supportive information of the potential meaningfulness of the findings.

So to summarize the exacerbation results, tiotropium HandiHaler 18 micrograms reduces exacerbations of COPD and this is seen as a primary outcome in the Veterans' Affairs trial of 1,829 patients. The results in the VA study confirmed what we initially saw in the registration trial and we see a consistency across subgroups.

While the UPLIFT trial did not show statistical significance on the primary outcome of rate of decline of FEV1, we're asking you to consider the data from nearly 6,000 patients participating for up to four years in your deliberations in this trial.

The UPLIFT trial is a very rich and large database that shows reductions of COPD and a remarkable consistency across subgroups. The findings are also consistent with what we've seen in the VA study, the registration trial, and, for that matter, other trials we have conducted.

There is also a consistency within the safety database when we've analyzed that and it is what we anticipated based on the biology of our understanding with an intervention that provides 24-hour airway patency and pharmacological lung volume reduction.

I'd like to now move on to discuss safety of tiotropium. The Phase III trials formed the basis of approval in the United States in January 2004. Since initial registration began in Europe

in 2002, there's an estimated over 16 million patient years of use in the community.

Now, over this time, we've continued to follow safety through ongoing and completed trials, through literature review, observational studies and analysis of spontaneous reports. All of this is part of our routine pharmacovigilance activities for which we periodically report information into regulatory authorities.

In March 2008, the FDA posted information in an early communication based on information voluntarily forwarded by Boehringer Ingelheim. Based on data from a pooled clinical trial database, the incidence rate for stroke was 0.8 events per 100 patient years of time at risk in the tiotropium group compared to 0.6 in the placebo group. The FDA described that the UPLIFT trial would provide further data regarding stroke and further insights regarding safety.

The early communication was updated in October 2008. The FDA noted that upon their preliminary review of the UPLIFT trial, there did

not appear to be an increased risk for stroke with tiotropium. The FDA also noted that there had been two recent publications that associated a potential risk for mortality in cardiovascular events with inhaled anticholinergics, including tiotropium.

So it's within this context and, of course, the general public health issues that are raised that I'll be presenting my next series of slides.

So based on the early communications, there were three safety issues that had been identified -- fatal events, cardiovascular events, and stroke. Now, with regard to the identification of fatal events, that was described in the context of a publication of an observational study with ipratropium, not tiotropium.

The mention of cardiovascular events in the early communication was based on the publication of a meta analysis that had both ipratropium and tiotropium. Stroke, of course, was based upon the information that Boehringer Ingelheim had provided from a clinical trial safety

database.

So for observational studies, I will describe summary results of all cause mortality from three observational reports performed or sponsored by Boehringer Ingelheim. For the issue of clinical trials, I'm going to predominantly rely on the largest single trial we have with tiotropium, which is the UPLIFT trial, to specifically address each of the three safety issues.

I'll also show additional data based on the entire pooled HandiHaler clinical trial database and supplement this with the information from the alternative formulation of tiotropium, not available in the U.S., tiotropium Respimat.

There are three reports of observational studies that are described in detail in your briefing document. The first is a study conducted in Denmark using their health care registries and a cohort design. The adjusted hazard ratio for all cause mortality, tiotropium relative to the control, was 0.77, with an upper limit of the

confidence interval of 0.91.

The second study used the Health Information Network database from the U.K., cohort design, with a hazard ratio of 0.70 for all cause mortality and an upper limit, again, of less than 1.

The third study used the ICPI PHARMO database in the Netherlands. This was conducted by investigators at Erasmus University. The hazard ratio in this case, control study was 0.76 with wider confidence intervals.

Additionally, there have been two independent recent publications of observational studies, which I have listed here. The fourth line refers to databases from the Ontario Health Care System in Canada. It was a cohort design and the adjusted hazard ratio was 0.80 and, again, the upper limit of the confidence interval being less than 1.

Now, the last report is actually from the same database and investigators that was noted in the observational report publication in the early

communication.

In this case, whereas they used ipratropium first, this is with tiotropium, and tiotropium in combination with inhaled steroids and long-acting beta agonists, showed a reduction in the hazard ratio for all cause mortality of 0.60, but they also noted that this apparent benefit wasn't consistently seen across treatment groups.

Now, while there are certainly well recognized limitations with all observational reports, what we can say is that based on the information, there doesn't appear to be an increased risk or a safety signal suggesting an increased for all cause mortality with tiotropium.

I'd like to now move on to the issue of mortality within clinical trials, and I'm going to rely on the UPLIFT trial. For the UPLIFT trial, we conducted several analyses on mortality, all of which are included in your briefing document.

The next series of slides is an analysis based on the intention to treat cohort, including the vital status information from prematurely

discontinued patients up until the end of the protocol-defined treatment period, which we refer to as Day 1440.

So the figure shows the probability of all cause mortality on the vertical axis and time through 48 months on the horizontal axis. Green, again, is tiotropium, yellow is placebo.

At the bottom here, I've placed a number of fatal cases just to emphasize the size of the database that we're looking at in the UPLIFT trial. There were 491 fatal cases in the placebo group and 430 fatal cases in the tiotropium group. This also reflects the unfortunate morbidity and mortality that is a feature of this chronic disease.

So over 900 cases. The hazard ratio is 0.87, indicating a 13 percent reduction in risk, with a nominal P value of 0.03. I also want to emphasize that we are not seeking a claim on survival and that the purpose of displaying this data is to specifically address the issue identified in the early communication regarding mortality.

We have also conducted subgroup analysis of all cause mortality to see if there was a subgroup who might be considered an increased risk. The subgroups displayed in this figure are age, gender, smoking behavior, and concomitant use of respiratory medications; again, long-acting beta agonists, inhaled steroids, the combination and the two, and anticholinergics. There does not appear to be a subgroup who one would consider at increased risk of a fatal event. Further subgroups are shown according to Gold Stage of severity, moderate, severe and very severe disease, as well as regions.

Overall, the UPLIFT data, as a large, single clinical trial, does not indicate that there is an increased risk of tiotropium HandiHaler with all cause mortality in patients with COPD.

I'd like to now move on to the second safety issue identified in the early communication, which is cardiovascular events. So this is a summary table showing adverse events, serious adverse events, and fatal adverse events under the

cardiac system organ class and the vascular system organ class.

N refers to number of patients with an event, IR is the incidence rate per 100 patient years' exposure, RD is the incidence rate difference tiotropium to placebo. This is the same analysis and the same type of display as I've shown you with low respiratory tract events and for respiratory failure.

So examining the patterns here for the incidence rates in the tiotropium group compared to the placebo group, and there doesn't appear to be an increased risk. Indeed, for most of these variables, the incidence rate is slightly lower in the tiotropium group and that's reflected by most of these rate differences being negative five of the six. And for serious cardiac adverse events and for fatal vascular events, actually, the upper limit of the confidence interval excludes zero.

This table shows categories of cardiac events. These categories have been determined by taking clinically similar preferred terms and

placing them together. For example, for myocardial infarction, we've added the specific terms "acute myocardial infarction" and "myocardial infarction," which are actually separate preferred terms. So that's been combined and all of the terms in myocardial infarction have been included in the broader category of ischemic heart disease.

Looking across, again, of the patterns of incidence rates in tiotropium versus placebo, overall, there is a lower incidence rate for these cardiac events, and these categories of cardiac events with the tiotropium group, there is a slight positive for superventricular tachycardia, which is a known and expected event with inhaled anticholinergics. In your briefing document, there are identical tables for serious cardiac adverse events and fatal cardiac adverse events, and the patterns are the same.

So when we consider the UPLIFT trial, we do not see an associated increased risk of cardiac or vascular events with tiotropium HandiHaler.

I'd like to now move to the third safety

issue identified in the early communication, which is stroke. This is a summary of adverse events, serious adverse events, and fatal adverse events for stroke from the UPLIFT trial.

I would like to mention that the analysis approach here and the approach to stroke is identical to what was submitted earlier to the FDA that formed the basis of the early communication. The only difference here, or the major difference, is that there are 162 cases of stroke, which is approximately four times the database that was originally submitted. Looking across, again, the incidence rates, the incidence rate differences indicates that there is no associated increased risk of tiotropium HandiHaler with stroke.

As an additional step, we have analyzed the composite endpoints of major adverse cardiovascular events. This composite endpoint is composed of adding all fatal events in the cardiac system organ class, all fatal events in the vascular system organ class, fatal and nonfatal MI, fatal and nonfatal stroke, as well as the preferred

term sudden death, cardiac death and sudden cardiac death. These latter three terms are not coded as a primary path to either cardiac or vascular and, hence, have been included here. We also have a subgroup of major adverse cardiovascular events, which is fatal cardiovascular events.

In this analysis, there are over 450 patients with a major cardiovascular event. The incidence rate for both of these endpoints is lower in the tiotropium group compared to the placebo group, reflected by negative rate differences and upper limits of the confidence interval that are less than zero.

We have also gone back to the large tiotropium clinical trial safety database. As a reminder, this includes 26 trials, including all of these trials. It involves over 17,000 patients and an estimated 12,000 patient years of exposure to tiotropium HandiHaler 18 micrograms in clinical trials.

In the next two slides, I'll summarize key cardiovascular endpoints. We've looked at the

entire database. There is no evidence of an increased risk for all cause mortality and the same applies to cardiovascular events.

This is a table that is similar to what I've just shown you from UPLIFT, with adverse events, serious adverse events, and fatal adverse events for the cardiac and vascular system organ classes. The difference here is I've just added in the stroke endpoint.

Overall, looking at the incidence rates compared to the placebo group, there isn't a pattern suggesting an increased risk associated with tiotropium HandiHaler. Indeed, for cardiac events as a whole, all adverse events or serious cardiac adverse events or fatal cardiac adverse events, the upper limit of the confidence interval excludes zero.

This is a table using the entire tiotropium HandiHaler clinical trial database for the composite endpoints of major adverse cardiovascular events and fatal cardiovascular events. So there is more information compared to

the UPLIFT trial alone, but the patterns are identical, with lower incidence rates and negative rate differences. It is acknowledged, however, that the major contributor to this pooled clinical trial database for these endpoints is the UPLIFT trial. So I've displayed here the UPLIFT trial for comparison.

Just to note, the UPLIFT trial, as a single, long-term, large, prospective study, not only shows lower incidence rates for these endpoints, but, again, upper limits of the confidence intervals that exclude zero, implying a relatively high degree of confidence that excludes an increased risk for major adverse cardiovascular events and fatal cardiovascular events.

So to summarize, the updated safety database provided by the UPLIFT trial specifically addresses each of the concerns regarding safety that have been identified or raised in the early communication in that the data do not demonstrate an increased risk for fatal events, cardiovascular events or stroke with tiotropium HandiHaler in

patients with COPD.

Earlier in the presentation, I referred to the alternative formulation of tiotropium, tiotropium Respimat, which is not available in the United States, but was approved in Europe in 2007.

Tiotropium Respimat 5 micrograms, the approved formulation in Europe, was developed to have a similar pharmacokinetic and pharmacodynamic profile as tiotropium HandiHaler 18 micrograms. Now, although there are differences in dosing from each device, the actual lung dose is similar and this simply reflects the improved efficiency in the Respimat delivery system.

There are five trials with tiotropium Respimat that meet the same criteria as we've used for pooling of the tiotropium HandiHaler clinical trial database. Three of these trials are one year in duration. The trials with tiotropium Respimat have shown that tiotropium Respimat improves lung function, provides sustained improvements in symptoms, and reduces exacerbations of COPD.

Regarding safety, we have observed an

unexpected numerical increase in fatal events in the tiotropium Respimat arm compared to the matching placebo, which you are being asked to consider in your deliberations today.

Now, just as a quick example of the efficacy results, these are exacerbation findings from the largest one-year tiotropium Respimat trial, Trial 205.372. The figures are for exacerbations which are identical to what I've displayed for the VA trial and the UPLIFT trial.

The figure on the left shows the probability of exacerbation -- again, green is tiotropium, yellow is placebo -- with a significant reduction in risk for an exacerbation with tiotropium Respimat. The figure on the right is the probability of a hospitalized exacerbation tiotropium versus placebo. Again, there is a reduced risk for hospitalized events with tiotropium Respimat.

This is a table summarizing all cause mortality observed in the three one-year trials, as well as a recently unblinded six-month trial with

the tiotropium Respimat 5 microgram arm that is included in your briefing document.

I want to note that 254 and 255 were the one-year trials that were the basis of registration in Europe and they also included a 10 microgram formulation as part of dose finding.

All of these trials in this table include vital status information of prematurely discontinued patients, although it was a retrospective collection in Trials 254 and 255. This display shows number of events, incidence rate per 100 patient years of exposure, and incidence rate differences.

As you can see, there are more cases, more fatal cases in the tiotropium Respimat arm. However, among the trials, there are some differences in the patterns, as well as variability in the incidence rate estimates; for example, an incident rate estimate as low as 0.66 in one of the tiotropium and the placebo Respimat arm in one of the trials.

Now, overall, the numbers are somewhat

smaller compared to the HandiHaler formulation. Indeed, in UPLIFT alone, there are over 900 fatal events. But as a comparison to the HandiHaler formulation, I've displayed UPLIFT data, but truncated at one year to have a similar timeframe as the other one-year trial. So with the HandiHaler formulation in UPLIFT, there were six fewer deaths at one year. However, it is also recognized that all of these confidence internals do overlap.

We have analyzed the composite endpoints of major adverse cardiovascular events and fatal cardiovascular events from the tiotropium Respimat 5 microgram trials. Now, this is a pooled analysis and, as I stated earlier, we have five trials that meet the same criteria as we used for pooling in the HandiHaler formulation, and that is displayed in this table.

As a comparison, I've now displayed the pooled HandiHaler analysis, which I have shown in a previous slide. These are different pooled analyses and the major difference is that the

trials here go up to one year. However, the HandiHaler formulation does include the UPLIFT trial, which is a database up to four years.

The rate difference for major adverse cardiovascular events is negative in the Respimat trials and in the HandiHaler trials, implying lower incidence rates in the tiotropium formulation, although the magnitude is larger, certainly here, and there were significantly more patients and an upper limit of the confidence interval excluding zero.

For the endpoint of fatal cardiovascular events, the direction of the differences are different. So a positive rate difference based on 13 versus 25 cases, a higher incidence rate here, and a negative rate difference with the HandiHaler formulation based on over 200 cases.

I've highlighted the actual incidence rates for the four treatment groups and it's somewhat similar in the tiotropium active formulation, but the major difference appears to be with the 13 cases and 0.55 events per 100 patient

years at risk with the tiotropium Respimat arm -- sorry -- the placebo Respimat arm.

We've also looked at the endpoints of stroke from the pooled clinical trial analysis. The display is similar to what I've shown previously, where there's adverse events, serious adverse events, and fatal adverse events for the endpoint of stroke.

This is a smaller dataset compared to the HandiHaler formulation. However, the patterns are the same in that when we look at the number of events and the incidence rates and rate differences, there doesn't appear to be an increased risk of stroke with tiotropium Respimat.

So to summarize, we have observed an unexpected numerical increase in fatal events in the tiotropium Respimat trials with tiotropium Respimat compared to the matching placebo.

We carefully examined, reviewed, analyzed, scrutinized all of the available data from the tiotropium Respimat formulation and, for that matter, the HandiHaler formulation. Based on

our review, we cannot determine a mechanistic rationale for the apparent safety differences based on our understanding of the pharmacology of the substance, the pharmacokinetics and the excipients of each formulation.

Now, it is possible that there might be some prior related factor that could be contributing to the differences in the reporting of adverse events among these trials; for example, there is a differential and preferential withdrawal of the most severe COPD patients in the placebo group, but it's difficult to be certain as to the contribution of such phenomena when looking retrospectively.

Nevertheless, Boehringer Ingelheim is committed to fully evaluating these results and we are planning to initiate a large long-term study early in 2010 to evaluate the relative benefits of tiotropium Respimat and safety compared to tiotropium HandiHaler.

I'd like to now return to the focus of my presentation today and, indeed, the major topic of

discussion in this Advisory Committee, and that's with the approved formulation of tiotropium in the United States, tiotropium HandiHaler 18 micrograms in the treatment of COPD.

The data from tiotropium indicates that tiotropium HandiHaler, 18 micrograms, based on a large, extensive clinical trial program, demonstrates that there are reductions in exacerbations with tiotropium HandiHaler, and this is observed from a primary outcome study, a VA study involving 1,829 patients.

It's supported by information from a very large, long-term clinical trial, the UPLIFT trial. We see the results with consistency across numerous subgroups, and further support when we look at the consistency of the adverse events reported into the clinical trial safety database.

Additionally, when we examined the safety database with UPLIFT alone and in combination with the remainder of our clinical trials, we did not see an association with tiotropium HandiHaler and all cause mortality, cardiovascular events and

stroke.

So in conclusion, the data presented here today provides substantial and meaningful evidence that support the proposed revisions to the Spiriva HandiHaler label. Specifically, we are seeking to add reductions in exacerbations to the indication statement for Spiriva HandiHaler and insert the applicable data from both clinical trials into the clinical study section.

As described by Dr. Tashkin, exacerbations of COPD are meaningful events that can result in prolonged and profound effects and impacts on the lives of patients, as well as their families. Information regarding exacerbations and treatment effects of exacerbations constitutes meaningful information for patients and prescribers when assessing the safety and benefits of Spiriva HandiHaler and, for that matter, when making treatment decisions in COPD.

Finally, we are seeking confirmation today that the updated safety information provided by the UPLIFT trial addresses the issues raised in

the early communication and that the data do not demonstrate an association of increased risk for fatal events, cardiovascular events and stroke with Spiriva HandiHaler in the treatment of COPD.

I'd like to thank you today for the opportunity of presenting the tiotropium data.

DR. BRANTLY: Thank you very much. I would like to invite members of the committee to address questions to the sponsor at this point. Let me remind you, for the purpose of keeping track of our comments, that you please read your name into the record prior to your comment.

Sean?

DR. HENNESSY: Thank you. I have a comment and two questions for Dr. Kesten. One is that my wife used to work in pharmaceutical advertising and when I would counsel her on trying to make small differences look big, I would talk about cutting off vertical axes on benefits, which was done in many of the slides here. So, consequently, a 13 percent relative reduction looks much more impressive than a 4.4 percent absolute

reduction. That was the comment.

The two questions are, on the VA study, slide 31 shows patients that have a lower FEV1, indicating worse function, appear to have better benefit. Yet, slide 46, from the other study, the name of which escapes me, shows that a lower Gold Stage was associated with less benefit. I'm wondering if the FEV sub-analysis was done on the UPLIFT trial and if those two observations can be rectified.

DR. KESTEN: So the question relates to FEV1 and, specifically, you're referring to the lower stages, the more severe patients, or the higher stage? Just to clarify.

DR. HENNESSY: Right. Your slide 31 --

DR. KESTEN: Yes, slide 31.

Can I have that slide up, please?

DR. HENNESSY: -- which is from the VA trial shows that if you had worse FEV1, you appeared to benefit more from the drug; is that right?

DR. KESTEN: Yes.

DR. HENNESSY: Yet, in the UPLIFT trial, you don't present results stratified by FEV1, but you do by Gold, and that's slide 46. And that appears to show, if I'm reading it right, that patients with less severe disease benefitted more.

Am I understanding that correctly?

DR. KESTEN: Yes. The Gold Stage is based on FEV1 severity and there are slight differences between ATS and Gold Stage. Gold Stage is post-bronchodilator and the cutoff is 30 percent versus 35 percent in the VA study, so similar. But your observation is correct that the benefits were not observed to the extent that we see in the VA study.

DR. HENNESSY: It seems to go the opposite way, though, right?

DR. KESTEN: Yes. For example, again -- can I have the VA slide just to highlight that?

The FEV1 differences are most apparent in this category of disease. But in the UPLIFT trial -- can I have the UPLIFT hazard ratios according to Gold Stage, slide up? The benefits appear to be in

the larger population here.

The UPLIFT trial, these patients are about 10 percent of the population, but you're correct that we didn't see the same magnitude of benefit. There are wider confidence intervals that do overlap.

We've tried to look at other means to identify this severe population of patients to look for supportive data. The UPLIFT data was designed to look at the COPD cohort as a whole, showing those reductions.

DR. HENNESSY: Let me ask you specifically. Did you stratify UPLIFT based on baseline FEV1?

DR. KESTEN: Yes. That's this slide.

DR. HENNESSY: So Gold Stage is the same as FEV1.

DR. KESTEN: Yes. I'm sorry. I'd like to clarify, if I may. So Gold Stage of severity is the recent classification that's identified internationally for using FEV1 severity as a means for characterizing patients with moderate, severe

and very severe disease.

So, for example, Gold Stage 2 moderate disease is patients with an FEV1 greater than 50 percent post-bronchodilator, two is 30 to 50, and four is less than 30 percent. So it's a little different from the ATS staging which was used then, but the concept is the same and the values are close.

DR. HENNESSY: I'm still puzzled as to why the trend goes in opposite directions in the two trials. I won't belabor the point anymore.

But my third question is, did you do a pooled analysis of all cause death across the different Respimat studies like you had done pooled analyses of other outcomes, and if so, can we see those results?

DR. KESTEN: First, if I may finish about the FEV1 severity to address that and then go to all cause mortality for Respimat.

Could I have the slide from the safety database on FEV1 less than 35 percent?

So what we've done for that is we had a

smaller cohort for the more severe patients in UPLIFT and went back to our pooled clinical trial safety database and looked for adverse event reporting to see if we found discrepant findings or supportive findings.

So this is a table based on reports by investigators of exacerbations with a narrow definition, exacerbations with a broader definition, such as including worsening of bronchitis, and then exacerbation when you included pneumonia for adverse events, serious adverse events and fatal adverse events for this cohort.

So now we have a lot more patients. And this is pre-bronchodilator FEV1 less than 30 percent. The display is number of patients, incidence rates and rate differences for these observations. And across the categories, for adverse events and serious adverse events, we're seeing negative rate differences, indicating that there is data suggesting a lower risk for exacerbations as an adverse event or serious adverse event with severe disease.

Now, with regard to your second question regarding mortality in the Respimat trials, I'd like to refer to Dr. Bernd Disse, who has been involved with the development program of Respimat since the very beginning, who is therapeutic area head for respiratory.

DR. DISSE: My name is Bernd Disse. I am area head for Respiratory Medicine at Boehringer Ingelheim. If I understand your question correctly as addressed, it is if the mortality in the Respimat trial set is Gold Stage or it's severity dependent.

DR. HENNESSY: No. I'm sorry. That wasn't my question. My question was there is a slide presenting all cause mortality differences from the individual Respimat trials, but I didn't see one that pooled across all of those.

I wanted to know if there was a summary effective measure for all cause mortality across those trials with the 95 percent confidence interval, because oftentimes, individual studies will show a trend and not be statistically

significant, but when you pool across them, they will be.

DR. DISSE: Yes. This has been done and I can even give the numbers, as I recall them.

DR. HENNESSY: You don't have a slide for it?

DR. DISSE: Yes, certainly, but it needs to be dug out. In the group safety, for adverse events, let me give you the numbers. They are reported in the briefing document.

From the pooled dataset, the rate ratio was 1.33. The confidence interval included one and the P value was about 0.15. So that is the pooled result. We will provide the slide after the break.

DR. HENNESSY: Thank you.

DR. BRANTLY: Les?

DR. HENDELES: Leslie Hendeles. Two questions. Interestingly, the data does show that tiotropium adds bronchodilator effect in patients who are already on bronchodilators, which might be important for this group who has such a poor response to bronchodilators.

The two questions I have, first of all, how many patients have to be treated to prevent one exacerbation?

DR. KESTEN: Would you like me to address the first question?

DR. HENDELES: Sure.

DR. KESTEN: Okay. The issue is regarding NNT. I'll give you the answer and then I'd like to comment on it. The NNT from the UPLIFT trial is between 16 and 24, depending upon the timeframe.

I think one of the issues of NNT is to consider some of the limitations, because you have to recognize the timeframe. So are you talking about a number you need to treat for six months, three months, one year, two years, three years, as well as some of the issues regarding study design, concomitant medication use, which can influence the interpretation of the NNT.

DR. HENDELES: My second question is, how did you measure it here and in the UPLIFT study?

DR. KESTEN: In the trial, we looked at

capsule counts and patients were asked to return their capsules to clinic visits.

DR. HENDELES: Do you have a mean value with a range on what the adherence was?

DR. KESTEN: Approximately 80 percent adherence at four years.

DR. HENDELES: Thank you.

DR. KESTEN: That was over 90 percent at one year.

DR. HONSINGER: Richard Honsinger. As I look at the data, if it's just a bronchodilator effect, I'd like to see what the results were after the patients stopped. Do you have any information on pulmonary function tests or availability of data after the patients have completed their course of medications?

As we're seeing a bronchodilator effect, we might expect them to go back to the norm line, like we see on the slides 38 and 39.

DR. KESTEN: One, we did request, actually, in the UPLIFT trial that patient return to clinic with a 30-day follow-up or washout

period. So it's somewhat difficult to interpret. I'll give you the results.

The bronchodilator effects went down, approaching to the mean of both groups, not quite the same. But the issue on that is the differential withdrawal of patients over four years, so that we have a substantially lower number of patients at the end of four years who agreed to come in again for a 30-day follow-up. So it's limited in what we can interpret, but it does appear that the effect wanes over 30 days.

DR. NEWMAN: I have a question about comparative study design, specifically related to the mortality question and the exclusion criteria that are used in the Respimat studies as compared to the UPLIFT.

Could you please comment on -- I know you had exclusion for prior cardiovascular disease, arrhythmias, et cetera. Are there any differences in those exclusion criteria that might lead us to suspect some differences -- to explain some of the differences that are being seen in mortality?

DR. KESTEN: Actually, just to clarify, I'll begin by clarifying what the exclusion criteria were for cardiac. The exclusion criteria were myocardial infarction the preceding six months, hospitalization for congestive heart failure in the preceding year, and unstable arrhythmia or life-threatening arrhythmia. So someone on stable arrhythmia medications would be included.

The inclusion and exclusion criteria were fairly similar, just about the same for the UPLIFT trial and the largest one-year Respimat trial.

DR. BRANTLY: Dr. Terry?

DR. TERRY: Peter Terry. There appears to be, at first glance, a reduced number of exacerbations in the tiotropium group. I've been involved in a number of studies, however, where it turned out that the average number of visits that the patients had in the experimental group was different than the control group and that that appeared to have influenced outcome.

So I wanted to know, what was the average

number of visits in the experimental group versus the control group? Did you track changes in use of other bronchodilators and/or steroids over time to see if there were changes in the groups?

DR. KESTEN: So two questions. The first relates to additional health care utilization in the UPLIFT trial. We did not track the additional unscheduled visits. We can say it looked at not only the number of exacerbations, but the number of antibiotic exacerbations, the number of steroid exacerbations, the number of hospitalizations. So I can't really give you the information on scheduled visits.

For the second question, which was concomitant respiratory medication, if we look at the entire trial overall across and at the end, there seems to be similar use of other respiratory medications.

Now, the exception was where the patients came into the trial not on maintenance medications and then in that population, comparing the tiotropium group to placebo, there actually was a

delay in the time to the prescription of first maintenance medication.

The other groups, which have already had the medications, are confounded groups and we didn't overall see much difference.

DR. BRANTLY: Dr. Platts-Mills?

DR. PLATTS-MILLS: Tom Platts-Mills. Thank you. I have two minor points and then a serious question.

Are the strokes consistently bleeding or clotting? Can you see data of that kind?

DR. KESTEN: I'm sorry. Could you repeat the question?

DR. PLATTS-MILLS: In the strokes, presumably, they all got head CTs. Were they bleeding or clotting or is there any difference between the two groups?

DR. KESTEN: So the question relates to the etiology of stroke, hemorrhagic or ischemic. Unfortunately, not all the cases had CT scans or not all the cases, when we saw the narratives, recorded CT or other imaging.

We have actually looked at the standardized medical queries of ischemic events versus hemorrhagic events. It is limited. I don't want to over-interpret that data, but we don't see any pattern suggesting increased risk with one versus the other.

DR. PLATTS-MILLS: The second question, I may have missed it in the data, but there's another treatment for COPD, which is pulmonary rehab. Pulmonary rehab, was that standardized? Both inpatient and outpatient pulmonary rehab, was it standardized and was it different in the Respimat study than in the UPLIFT study?

DR. KESTEN: I'm certainly, as a pulmonologist, very glad you raised it, because pulmonary rehab is one of the most important therapies in these patients and I wholeheartedly agree with you.

We didn't capture pulmonary rehab during the UPLIFT trial. What we did is patients who entered the UPLIFT trial shouldn't have been in a pulmonary rehab program at that point. Then we

randomized them and we wanted to try to create a real world setting and let the patients go into the trial as they would and have their prescriptions and their treatments as they would over four years.

With the variabilities, we still were able to see these reductions in exacerbations, reduced risk in lower respiratory morbidity, and reduced risk for hospitalized exacerbations.

DR. PLATTS-MILLS: Dr. Tashkin provoked that question because he actually had in one of his slides decreased physical activity and the obvious possible cardiovascular effect.

Can I ask a third question? That is, do you know anything about the nature of the exacerbations? That is, exacerbations of COPD could be viral, they could be bacterial or they could be fungal.

I don't know. Do you have any information? Was any attempt made to identify those, because some of the -- there's old history about fungal and sometimes people who get fungus in their lungs with COPD become very resistant to

treatment. Was there any attempt to identify those cases and could it explain differences?

DR. KESTEN: No. We did not, in this large trial of four years, attempt to capture microbiology or ask the investigators to record any sputum evaluation. So I can't specifically address that, although what I can tell you is that we've looked at the antibiotic treatments versus steroid versus combination, which sometimes gives some thought into physician prescribing and we saw reductions in the risk for an antibiotic-treated exacerbation and both the steroid-treated exacerbation.

Actually, if I may, I just want to come back to your last point of rehab, because you mentioned it in the context of Dr. Tashkin's presentation. We have conducted and published a study where we gave the combination of tiotropium plus pulmonary rehab versus pulmonary rehab alone.

That was published by Rich Casaburi and showed that having tiotropium onboard amplified the benefits in terms of exercise tolerance at the end

of rehab with a rehab program. It supports what you're saying and certainly supports what Dr. Tashkin was saying.

DR. BRANTLY: Other questions? Dr. Knoell?

DR. KNOELL: Daren Knoell. A couple of simple questions. This is related to the compound itself. My understanding is it's a charged quaternary ammonium, so it's not going to be appreciably absorbed with repeated administration.

But you commented that with the Respimat comparison, in particular, you guys have conducted extensive analyses and found no evidence to suggest that it's a difference in perhaps drug absorption. So that's one point of just clarification, if you can expand upon that.

Then the second question, or first question, is now that you have a four-year trial and thousands of patients, following those patients in any way kinetically, do you have any evidence to raise concern or put to rest that with chronic use over years, that this compound could be absorbed at

appreciate levels to account for systemic toxicity?

DR. KESTEN: Well, the pharmacokinetic questions, for the long-term and also between the formulation, I'm going to also ask, again, Dr. Disse to address that. He also has a background in pharmacology.

But while he's coming up, I just want to say that we did not see anything in terms of the adverse event profile over time in the UPLIFT trial. So the effects on exacerbations, the analysis of mortality didn't suggest that there would be anything clinically meaningful. We continue to see the effects as we had at the beginning of the trial and the end of the trial.

DR. DISSE: As you rightly pointed out, this is a quaternary ammonium drug and, as such, it has a very low absorption from the gastrointestinal tract. It is about 10 percent, then by the first pause, it's reduced to 3 percent.

But all drug that reaches the lung, that's our experience, becomes absorbed, which means from the HandiHaler, which is about 18

micrograms in the capsule, some 10 micrograms leave the device. Then the fine particle fraction then goes to the lung. It is has to be calculated, and this makes a lung dose of 3 micrograms and that dose becomes absorbed.

Similarly, the Respimat, 5 micrograms come out of the device, with calculating the fine particle accessible to the airways and the lungs, some 3 micrograms is the lung dose and that becomes completely absorbed.

So we have compared, in pharmacokinetic studies, the two devices. And there's four weeks treatment, fully into steady-state, then evaluated the systemic levels. And the excretion in urine over 24 hours is an appropriate measure, reflecting total exposure.

With that, studies in Caucasian patients have shown about a 1.2 to 1.3-fold exposure following Respimat. In Asian patients, surprisingly, it was equivalent, so similar exposure. Our conclusion at this point is the exposure following Respimat is similar, maybe up to

1.3-fold higher in total exposure.

Your second question is a very difficult one, because pharmacokinetics, over time, hasn't been done. But following adverse event profiles over time doesn't give an indication that adverse events may increase.

There is one point to be made. Certainly, this drug is slowly equilibrating, which means it takes some time to reach steady-state, about two to three weeks, and typical systemic anticholinergic events then come up after this period in time, but rarely before. Other than that, we are not aware of any time sequence or delayed toxicity effect.

DR. BRANTLY: Dr. Platts-Mills?

DR. PLATTS-MILLS: Can I ask another related question? There was a period in the '80s when we were using another anticholinergic. It's either called glycopyrrolate or paroglycolate; glycopyrrolate in a nebulized form. You don't have any data comparing tiotropium to glycopyrrolate.

DR. DISSE: No. A direct comparison has

never been done. From published literature, you can conclude that glycopyrrolate is also a longer-acting anticholinergic. Maybe it's in the middle between ipratropium and tiotropium. But a direct comparison hasn't been done.

DR. BRANTLY: I have a couple questions, also. Dr. Brantly. The first question is, it was mentioned that one of the hypotheses for the mechanism for reduction of exacerbations is airway patency.

Are there any studies that directly provide data to support that particular hypothesis?

DR. KESTEN: Yes. So the question relates to the airway patency that was also mentioned by Dr. Tashkin and I'll ask Dr. Tashkin to also address this. There are two studies, the one that Dr. Tashkin referred to and then another study published in the European Respiratory Journal; a similar design where they took patients who came into the hospital with an exacerbation and followed their lung function, both spirometry and lung volumes, over time as they recovered.

You could see the pattern where there was quite dramatic improvements in lung volumes over time, suggesting that the event was accompanied by hyperinflation, which is, I think, well understood when you see any trigger reducing airway patency.

So that if you maintained airway patency, you are giving yourself more volume, more reserve, so that you can withstand an impact and intervention and the consequences, which not only can be symptoms, but also gas exchange abnormalities and other mechanical abnormalities and stress on a respiratory muscle.

I'd ask Dr. Tashkin, again, with his long history in clinical research, to elaborate.

DR. TASHKIN: Thank you for that question. The mechanism that I proposed in my presentation was really hypothetical. We really didn't have any direct proof, that that is the reason why a drug like tiotropium reduces exacerbations, but I think it's a reasonable hypothesis given the fact that tiotropium probably doesn't have any clinically meaningful anti-

inflammatory effects.

DR. BRANTLY: I have a second question regarding actually EKG findings in particularly the UPLIFT trial. That is, was there any safety signal with the EKG findings that would suggest some kind of a primary mechanism that we've seen in some of the previous reports?

DR. KESTEN: In the UPLIFT trial, we did not monitor ECGs during the trial. So I cannot comment on that. We have certainly done extensive ECG recordings in the development program, including Holter studies, and have not been able to see ECG findings.

In addition, we've done a thorough QT study with above therapeutic doses with 54 micrograms of HandiHaler and the thorough QT study was negative, as well.

DR. BRANTLY: Thank you very much.

Dr. Honsinger?

DR. HONSINGER: You've mentioned anticholinergic drugs and their absorption. As we look at the adverse events, were many of your

dropouts due to the adverse events of the effect on the cholinergic system?

I wouldn't expect people to have eye difficulty in this age group. Their lenses are already relatively stiff. I wouldn't expect them to notice much difference in their perspiration. But I would expect them to notice more difficulty with the cholinergic effect on the GI tract. I'd expect more constipation. I would expect more urinary symptoms, particularly in the men. As you get urinary symptoms, of course, you have incomplete emptying and then you have increased urinary tract infections.

Were these causes for dropouts?

DR. KESTEN: Yes. There were a small number of dropouts that we could attribute to anticholinergic effects, including those on the gastrointestinal tract and the urinary system, such as urinary retention.

However, overall, these events are relatively infrequent, quite infrequent, and if you look at the overall safety profile, there are more

discontinuations for adverse events, significantly more in the placebo group compared to the tiotropium group. But we did see the expected anticholinergic events with tiotropium.

DR. BRANTLY: Dr. Terry?

DR. TERRY: COPD was defined as emphysema and/or chronic bronchitis. Was the chronic bronchitis evenly distributed between the experimental and control groups?

DR. KESTEN: I cannot tell you with certainty on that, because we asked the physicians or the investigators to recruit patients with COPD that they have diagnosed, including chronic bronchitis and emphysema.

We did have a questionnaire going into the trial asking them to tic off chronic bronchitis, emphysema, not verified in any manner, just reporting it on entry. There was nothing there to suggest that, but, again, this is soft data. It's really taking all COPD patients according to a clinical diagnosis in the community.

DR. BRANTLY: Dr. Platts-Mills?

DR. PLATTS-MILLS: If we take the data that there has been a decrease in exacerbations, there are two possibilities. One is that the exacerbations are milder and, therefore, they don't end up needing an event or that they don't occur.

I don't know whether you have an opinion about which way, but if you really argue that it decreases exacerbations and they don't occur, then there should be a decreased rate of decline of lung function, and that you clearly didn't see.

DR. KESTEN: Those are both very, very interesting questions and you've asked me to a speculate a bit, so I'm more than pleased to do so.

So the issue of how is this drug working, which was, I think, your earlier question, is I do believe it is providing improvements in lung volumes and airflow and having that in a sustained manner that you can tolerate triggers or insults.

So in the true sense of the word, it doesn't prevent the trigger. It doesn't prevent the insult from occurring. I don't think other drugs will prevent the trigger or insult from

occurring. It's then your ability to tolerate what happens and the reserve that you have available that mitigates the consequences.

So if you have this much volume, your IRV has shrunk down so low that any further reduction will get you into hospital. But if you have more room, then maybe instead of hospital, you go to the physician's office. Instead of going to the physician's office, on one occasion, maybe you were able to treat yourself at home without consequences. So I think it all is consistent with an understanding.

Then the next question you had is regarding the rate of decline. Perhaps when we went into this, we were too ambitious and too aggressive in saying we're going to allow everything to have a real world setting here. If you're asking, again, me to speculate, I think that there are so many confounders when you're allowing medications and treatments and options to occur during four years, that it's very difficult to see patterns.

We have done a subgroup analysis, which we submitted to the American Thoracic Society just actually for the next year's meeting, where we're able to see, as a group, if you look at exacerbation frequency, there seemed to be a pattern with rate of decline, but not by treatment group, and I think there's a lot of confounding. And our understanding of the impact of exacerbations on rate of decline I think is still, if I may, a little too immature right now.

DR. BRANTLY: Dr. Knoell and then Dr. Wolfe.

DR. KNOELL: Daren Knoell. Again, I just wanted to follow-up with the last question. So, obviously, tiotropium affects the lung by causing bronchodilation. You show us nice evidence that that does happen, although it doesn't influence the rate.

Inflammation, we predict that this has nothing to do with inflammation, which I think kind of undermines what -- I shouldn't say undermine -- gets at what you were trying to tell us.

What I want to know is do you have any corollaries with this cohort where you've actually tracked indices of inflammation to see if there is modulation of that over time, in any way, shape or form?

DR. KESTEN: So the question is about inflammation and antimuscarinics and particularly tiotropium. There is data published in the basic science arena showing potential anti-inflammatory effects of anticholinergics, a number of studies actually published, including data with tiotropium, not in man, not in COPD, in Petrie dishes and animals. Clinical significance is entirely unclear and unknown. So there are some factors that may be at play that we don't understand.

As well, there is also the potential of indirect anti-inflammatory effects. For example, lung stretch actually is pro-inflammatory. We know that from the ICU literature. So if you're reducing hyperinflation and stretch on muscles, potentially, you have an indirect mechanism there. However, that being said, I think the major

mechanism is going to be the sustained airway patency and lung volume reduction.

Then to your last question, we did not measure inflammatory indices in that trial. We have some information from a smaller trial where IL6 was measured and IL8 and we didn't see any changes.

DR. BRANTLY: Dr. Wolfe, you have the last question here.

DR. WOLFE: This is a slight corollary of other people's questions and you've given a partial answer. You were overenthusiastic. But let's go back to UPLIFT study design.

You were, obviously, aware of what other medicines people were taking. What was the thinking on the part of the company as to designate as the co-primary endpoints the yearly rate of decline in pre and post-FEV1?

What was the mechanism that you thought would be operating in addition to or independent of the other meds? That's a question, because it was a mistake, as it turns out. But I just want to

hear, if possible, what the thinking was.

What did you think was going to happen?

DR. KESTEN: Thank you for that, because you always look back retrospectively at what you did and why you've done it. When we looked at the Phase III trials, we saw effects that were sustained with quality of life and we saw improvements in lung function with once daily dosing. We saw reductions in exacerbations. And we said, you know, if you put all this together and you're providing sustained airway patency, all these things must suggest maybe we do have something here that could have a long-term impact on the rate of decline, and other factors, such as if we believe that the drug may be influencing activity levels or exercise tolerance, the ability to participate.

We know that being a couch potato is not a good thing. So we put all that together and said, you know what, let's test this out. We had, also, a number of people coming to us who are reputable in the pulmonary field and said, "This is

a reasonable hypothesis to test."

It's really not much more than that into it and we sought to test it. We did include, though, other important clinical endpoints, because we did believe it's important to follow measurements of symptoms such as quality of life and exacerbations over the time and the lung function. So those were important secondaries for us.

DR. WOLFE: But, again, what did you think the mechanism was going to be for this differential -- didn't happen -- improvement in terms of FEV1? How did you think that was going to work in the face, again, of all these other medicines that you know people were taking?

DR. KESTEN: From the mechanistic point of view, the thinking was that airway collapse, which you have when you use short-acting agents or shorter-acting agents, over the long term, is pro-inflammatory and can have consequences. So the issue of airway collapse may influence into that and providing airway patency.

When you are reducing exacerbations, as we saw in the Phase III registration trial, which was a consistent finding, that it's possible that when you have more severe exacerbations, there are going to be long-term impacts on lung structure and function.

So by reducing them, preventing them or reducing the consequences, you may lower inflammatory burden and structural changes over time. So our thoughts were exacerbations, yes, that fits in; the issue of airway collapse, that fits in; and then these indirect measures of people indicating that their quality of life is better, that they're up and around, which also was thinking that this could impact long-term function in terms of getting the lungs open rather than having them around with constricted volumes.

DR. WOLFE: Just to follow-up. If that was what your thought was, that if I neutralize some of the inflammatory effects, why was there not more measurement, as I think you responded to someone, about inflammatory processes, such as, Dr.

Platts-Mills, looking at intercurrent infections, other measures of improvement in terms of inflammation?

DR. KESTEN: I think it's a valid point. The problem is if we had a single biomarker or even a few biomarkers which we could rely on for this disease, then I'd say, yes, we should have done that.

But the problem is, and even now, this day, unfortunately, we don't have reliable inflammatory markers, biomarkers that reflect the ongoing progression of the disease. We have biomarkers and cytokines that go up during certain periods. A lot of them are nonspecific. It's been a very complex disease to follow. So there wasn't a marker, and there still isn't one we can rely on. Actually, the NIH is funding several approaches. I know Dr. Chowdhury is involved in some of this.

Then there's the issue of, well, okay, you're doing this 6,000-patient trial over four years around the world. If you happen to show something on a biomarker, but you didn't actually

show anything clinically, people would just say, "Okay. Well, the biomarker didn't mean much."

DR. BRANTLY: I'm going to actually stop the discussion at this point and remind the committee that we have another opportunity during the discussion phase to ask the sponsor questions, if we wish.

We have now a 15-minute break. I'd like you to return at 10:20. Again, I also want to remind committee members that any discussion about the topic should be withheld. Thank you.

(Whereupon, a recess was taken.)

DR. BRANTLY: Thank you very much. We're going to begin right now. I'd like to begin with the FDA presentations. Dr. Michele will be presenting.

DR. MICHELE: Good morning. My name is Terri Michele and I'm adult pulmonologist with FDA in the Division of Pulmonary and Allergy Products. On behalf of the division, it's my pleasure to once again welcome you to Washington.

I'd like to thank Dr. Brantly and members

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of both the Pulmonary and Allergy Drug Advisory Committee, as well as our guest members from the Drug Safety and Risk Management Committee for being here today to share your expertise.

Over the next 45 minutes or so, I will be walking you through data from NDA 21-395 efficacy supplement for the approved drug product Spiriva HandiHaler, specifically focusing on information related to two primary objectives that you already heard from Dr. Chowdhury this morning; number one, to discuss the efficacy claim for the reduction of exacerbations in patients with chronic obstructive pulmonary disease; and, number two, to discuss three potential safety issues of stroke, myocardial infarction and cardiovascular mortality, and all cause mortality.

To begin, I will present some background information on Spiriva HandiHaler before moving on to efficacy data from the application. Here, I will cover two studies, Protocol 205.266, which I'll refer to as the VA study, because it was conducted in a Veterans' Affairs setting here in

the United States, and Protocol No. 205.235, which I'll refer to by its acronym of UPLIFT.

While I will touch on data for other efficacy claims in the application, the focus will be our first objective, COPD exacerbations. Next, I will move on to safety data from the UPLIFT trial, with a focus on our three potential safety issues of stroke, cardiovascular events, and all cause mortality.

For the final portion of the talk, I'm going to bring in data from the unapproved, but related product, Spiriva Respimat, that we feel is pertinent to a complete understanding of all of the safety issues for Spiriva HandiHaler. As you've already heard, Spiriva Respimat is another formulation of tiotropium bromide that's currently under development.

In order to avoid confusion with the Spiriva HandiHaler data, I will attempt to be very clear when I switch from talking about Spiriva HandiHaler to Spiriva Respimat and I'll highlight the differences between the products.

We will begin with the background. Spiriva HandiHaler is a dry powdered formulation of tiotropium bromide, which, as you know, is a long-acting anticholinergic. It was approved in the United States in January of 2004 as a once-daily dose of 18 micrograms.

Again, as you've heard, the current indication for Spiriva HandiHaler is for the long-term, once-daily maintenance treatment of bronchospasms associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema.

In this NDA supplement, the applicant has proposed the following efficacy claim: a description on the long-term effects of Spiriva HandiHaler on lung function, a reduction in exacerbations, which is the topic of this meeting. They've also proposed the following safety claims: a reduction in mortality, which was withdrawn by the applicant in July of this year, and a reduction in respiratory failure. And we'll touch on each of these claims during the discussion.

As I've already alluded to, there were two clinical trials submitted in support of this efficacy supplement. Trial No. 205.266, the VA study, was a six-month trial in approximately 1,800 patients conducted in the U.S. and Trial No. 205.235, the UPLIFT trial, was a four-year multinational study in about 6,000 patients.

With that background on the application, I will now turn your attention to the efficacy data for Spiriva HandiHaler. You've already heard from Dr. Kesten about the design of the VA study. I would just like to point out a few key similarities and differences between the VA study and other trials in the Spiriva HandiHaler dataset, in particular, UPLIFT.

Similar to other trials in the HandiHaler program, the VA study enrolled patients with moderate to severe COPD. Now, the VA study was a very real world study, with enrollment criteria that are the most liberal of any in the HandiHaler program.

Patients were permitted to be on any

pulmonary medication, except for anticholinergics. Oral steroids were permitted at a dose of up to 20 milligrams today in contrast to the UPLIFT study, where it was capped at 10 milligrams per day. And patients were also permitted to be on any duration oxygen therapy.

The study was designed to look at COPD exacerbations, with the two primary endpoints being the proportion of patients with a COPD exacerbation and the proportion of patients hospitalized for a COPD exacerbation.

I will not be presenting any safety data from the trial, because only serious adverse events were collected in this trial and the study was of relatively short duration, six months. You do have this data, however, available in your background packages.

In the VA study, a COPD exacerbation was defined as a complex of respiratory symptoms that were either increased or of new onset with a duration of greater than or equal to three days. These symptoms included cough, sputum, wheezing,

dyspnea and chest tightness.

There was also a requirement for treatment with either prescription antibiotics, systemic corticosteroids, hospitalization or any combination thereof.

The primary endpoints for this study are highlighted in the table in yellow and I've also listed several secondary endpoints that are pertinent to labeling claims. As you can see, the study met the first primary endpoint with a reduction in the proportion of patients with an exacerbation and a trend towards a decreased number of patients with hospitalizations due to exacerbation. The time to first exacerbation and the number of exacerbations per patient year were also reduced.

Moving on to the UPLIFT study, for understanding potential long-term impacts on function with tiotropium, again, you've already heard about the design from the sponsor.

I would just point out that this was a very large study, nearly 6,000 patients followed

for a substantive period of time, four years, resulting in more than doubling the available safety database for the Spiriva HandiHaler program, with randomized controlled, placebo controlled data.

Note also the order of the endpoints, which becomes important later on when you hear the discussion of statistical issues for the program. The study was designed to show a difference in disease progression, as you've heard, with co-primary endpoints of the yearly rate of decline in trough or pre-bronchodilator FEV1 and the yearly rate of decline in post-bronchodilator FEV1. There were a number of secondary COPD endpoints.

Similar to the VA trial, UPLIFT was also a real world study, evaluating patients with moderate to severe COPD. In general, inclusion criteria are similar across all the Spiriva programs. Slightly less liberal than the VA study, patients were limited to steroid use of less than 10 milligrams per day and oxygen use of less than 12 hours per day. Note also that there was no

criteria for previous exacerbations used to enrich the patient population.

I'd like to spend just a moment on concomitant medication use for the trial, because there was some confusion in the literature on this point. Patients were permitted to be on a stable dose of all concomitant medications, other than anticholinergics. All anticholinergics, including long-acting, short-acting, combination anticholinergics and intranasal agents were prohibited by the protocol. The only exception to this was during life-threatening COPD exacerbations, when patients could be on any and all medications, including anticholinergics.

Looking at the demographics of the patients enrolled in the UPLIFT trial, as you heard from the sponsor, the population was predominantly white males around 65 years of age and the pre-bronchodilator FEV1 was just over a liter. As you can see, the groups appear to be fairly well matched.

Again, as you've heard from the sponsor

and you can see from this table, there was no difference between treatment groups in either of the primary endpoints, either pre or post-bronchodilator, rate of decline in FEV1.

Now, because there was a hierarchical testing approach to multiplicity, this raises some statistical concerns regarding the secondary endpoints that you'll hear from Dr. Buenconsejo in the next talk.

It doesn't, however, detract from the clinical data on COPD exacerbations that I'm about to present. As a litmus test for this, one of the things that we look at is if the study had been designed in a different way, with COPD exacerbations as the first primary endpoint and rate of decline as the secondary endpoint, would the study have been conducted any differently, and based on the design of the study, we believe that it would not have been.

Also of interest in the rate of decline data is the subgroup analysis in which sustained smokers had the highest rate of decline in FEV1

compared to sustained quitters, with intermittent smokers being somewhere in between. This provides a nice marker of internal validity for the trial.

So lest the panel be left with the impression that Spiriva HandiHaler has no effect on lung function, I wanted to show the graphical representation of the data. This, again, is the same slide that you saw from Dr. Kesten.

So we have time here on the X axis, FEV1 on the Y axis, and Spiriva is here in the solid line, with placebo in the dotted line. You can see that the slopes of the lines look identical, but the difference between them, which represents about 90 to 100 milliliters, is the bronchodilator effect of the drug, which is maintained throughout the four-year treatment period. This information augments the one-year data that's available in the current Spiriva HandiHaler label.

The definition of COPD exacerbation in the UPLIFT trial was very similar to that of the VA trial. The exception was that sputum purulence was considered as a symptom rather than chest

tightness. In both trials, the onset of an exacerbation was defined by the first symptom and the end was defined by the investigator.

In the analysis, two exacerbations were considered to be distinct if more than seven days occurred between exacerbations. In the statistical analysis plan, although there were a number of secondary endpoints for COPD exacerbations, two were defined as key, the time to first exacerbation and the time to first exacerbation leading to hospitalization.

For comparison purposes, I've laid out this table in an identical format to what you saw for the VA study. In UPLIFT, Spiriva HandiHaler significantly increased the time to first exacerbation, with a difference of nearly four months, as well as the time to first exacerbation leading to hospitalization.

There was no difference in the proportion of patients with an exacerbation or the proportion of patients with hospitalization due to an exacerbation, which were the two primary endpoints

for the VA trial. This is not surprising, because the trials were designed to measure different aspects of COPD exacerbations. Since UPLIFT was a long-term trial, most of the patients who were susceptible to COPD exacerbation presumably had one, limiting the usefulness of this endpoint.

Looking at the data graphically, we have time here on the X axis and the probability of COPD exacerbations on then Y axis. You'll see that the curve that you just saw from the sponsor is the inverse of this.

You can see here a separation between the two curves, which begins at about six months, is wider by 12 months, and is maintained throughout the four-year treatment period.

So to summarize the efficacy data from this application, there was no difference between Spiriva HandiHaler and placebo in rate of decline of FEV1, although the bronchodilator effect was maintained. The VA and UPLIFT trials support benefit on COPD exacerbations. Then we'll ask you to weigh that against the statistical

considerations related to multiplicity.

Now that you've heard about efficacy, I'm going to switch gears and talk about safety. As I mentioned early on, I'm going to limit my discussion of safety data for Spiriva HandiHaler to the UPLIFT trial. Again, to remind you of the objectives of the meeting to think about as you hear the data, we'll focus on three potential safety concerns; stroke, cardiovascular events, and mortality.

Two of these potential safety signals, stroke and cardiovascular, are related to Spiriva HandiHaler and I will discuss them in this portion of the presentation on Spiriva HandiHaler.

A mortality imbalance in favor of placebo was observed in the Spiriva Respimat Phase III clinical trial. So while I'll present a substantial amount of mortality data from the UPLIFT trial in this portion of the presentation, we won't get to a full discussion of the mortality issue until we get to the Respimat data.

As you heard earlier, the potential

stroke signal comes from a pooled analysis of safety data from 29 placebo controlled trials, 25 with Spiriva Respimat and four with Spiriva -- that's backwards -- 25 with Spiriva HandiHaler and four with Spiriva Respimat, creating a combined dataset of over 13,500 patients.

As with most exploratory safety reviews, there were no corrections for multiplicity. In this analysis, the risk ratio for adverse events of combined stroke terms was 1.37 for tiotropium compared to placebo, translating to approximately two excess cases of stroke per 1,000 patient years on therapy. Note that the confidence intervals for this risk ratio include 1, indicating that the result is not statistically significant.

Based on this analysis and in keeping with the agency's mandate for increased transparency of ongoing safety reviews, FDA issued an early communication to the public regarding the potential signal of stroke in March of 2008.

The potential safety signal for adverse cardiovascular events comes from a meta analysis

published in September of 2008. The analysis included 17 randomized active and placebo controlled studies for the combined outcome of cardiovascular death, MI or stroke. Studies of both Spiriva HandiHaler and the short-acting anticholinergic, ipratropium, were included.

In this meta analysis, the risk ratio for major adverse cardiovascular events was reported as 1.58 for anticholinergics; remember, both HandiHaler and ipratropium versus control, both placebo and active. You will hear about the meta analysis in detail from Dr. Simone Pinheiro in the Office of Surveillance and Epidemiology.

Based on this meta analysis, FDA issued an early communication update for Spiriva HandiHaler to the public in October of 2008.

So now that we have an understanding of the potential safety signals involving Spiriva HandiHaler, I'll turn your attention to the safety design of the UPLIFT trial. All adverse events were collected in an ongoing fashion for the entire four-year study period of UPLIFT. Stroke and

combined stroke terms were predefined as an adverse event of interest in the statistical analysis plan.

All adverse events were monitored on a yearly basis by an independent data safety monitoring board. In addition to adverse event monitoring, the UPLIFT protocols prespecified prospective vital status collection, including cause of death on all discontinued patients.

So in other words, if a patient discontinued from the trial, he or she was followed-up until when the trial would have ended for that patient to determine if he was alive or dead.

A mortality adjudication committee, consisting of two pulmonologists and one cardiologist, independently assigned the cause of death for all 941 patients who died during the trial. The assignment was based on a review of primary data sources, such as narratives, death certificates, autopsy reports, and serious adverse event reports. Importantly, the committee assigned cause of death in predefined death categories

rather than by MedDRA preferred terms, which allowed prospective clinical grouping of categories, such as COPD, MI and stroke.

This table shows serious adverse events from the UPLIFT trial which occurred in at least 1 percent of patients in either treatment group. Note that the rates are unadjusted for patient years. You can see the most common serious adverse events were cardiac and pulmonary, with COPD exacerbations and pneumonia leading the list.

Serious adverse events were generally balanced between treatment groups. There was a slight increase in angina events, but coronary artery disease and myocardial infarction were numerically decreased relative to placebo. For pulmonary events, COPD exacerbations and respiratory failure were decreased in the Spiriva HandiHaler group compared to placebo.

Looking more closely at respiratory failure, there is a statistically significant decrease, with a risk ratio of 0.67 compared to placebo. Based on this finding, Boehringer

Ingelheim has requested a safety claim for reduction of respiratory failure.

However, there are several issues with this claim. First, the claim was not predefined in the protocol. As such, it's completely subject to interpretation by investigators at nearly 500 different sites in 37 countries.

Compounding the problem is the fact that there are multiple different MedDRA terms for respiratory failure. There is respiratory failure itself, which is what is shown here, and then there's acute respiratory failure and chronic respiratory failure, respiratory arrest, and a number of others. So finally, as this finding is part of the safety analysis, there is no correction for multiplicity.

Moving on to the previously identified potential safety signal of stroke, in the UPLIFT trial, the risk ratio for adverse events categorized under the combined stroke term was 0.93 for Spiriva HandiHaler compared to placebo -- I'm sorry -- 0.95, right here.

Stroke was a predefined category used by the Mortality Adjudication Committee, providing confidence that there are not other causes of fatal stroke coded under different terms. While these results are reassuring, the upper bound of the confidence interval is greater than 1. So a small increase in stroke in the Spiriva HandiHaler group cannot be ruled out.

Cardiovascular safety was assessed in the UPLIFT trial by evaluation of adverse events and cause of death. A post-hoc analysis evaluated the combined term of cardiovascular death, which included all serious adverse events with an outcome of death in the cardiac and vascular system organ classes, in addition to the term "sudden death" and "sudden cardiac death."

Myocardial infarction was not increased in the Spiriva HandiHaler group compared to placebo, with a risk ratio of 0.73. Note that the upper bound of the confidence interval is not greater than 1 for both adverse events and serious adverse events for MI.

Likewise, cardiovascular death was not increased in the UPLIFT trial, with a risk ratio of 0.73 and the upper bound of the confidence interval below 1.

This brings us to a discussion of mortality in the UPLIFT trial. As you can see from this table, overall mortality was significantly decreased in the Spiriva HandiHaler group compared to placebo, a finding that persisted across a variety of different analyses, with the risk ratio ranging from 0.83 to 0.89, depending on how it was calculated.

Just looking here, this first line is on treatment mortality at the end of the four-year treatment period. This includes the 30-day follow-up. This next line includes vital status out to the end of the planned treatment period, and this is vital status with a 30-day follow-up.

Based on this calculation, the difference in mortality rates translates to a number needed to treat of around 100 patients over a four-year period to prevent one death.

Here is the Kaplan-Meier plot of the mortality data for adjudicated on treatment death at day 1470. You've got time on the X axis, the probability of all cause death on the Y axis. You can see that the curves start to separate here at about 12 months and the separation is greater the longer you follow the patients out.

Over the four-year treatment period, the most frequent cause of death was COPD exacerbation, followed by lung cancer, which is not unexpected in this patient population. Comparing rates, you can see that there were fewer deaths in the Spiriva HandiHaler group compared to placebo for most categories, although the overall reduction was driven largely by a decrease in COPD exacerbations, which approached statistical significance with a risk ratio of 0.79. This gives a potential mechanism for the observed mortality reduction that's consistent with a postulated mechanism of the drug.

You've already seen this data, as well. This is a forest plot of the subgroup analysis for

mortality and, as you can see, the hazard ratio was generally favorable towards Spiriva across all subgroups, including age, gender, Gold Stage and concomitant medication use.

Note that the anticholinergic subgroup shown in this slide represents baseline use and do not imply concomitant anticholinergic use during the trial.

So in conclusion, the data do not suggest a stroke or cardiovascular safety signal in the UPLIFT trial, although some of the confidence intervals were rather wide. Overall, the data support a decrease in mortality in the Spiriva HandiHaler group compared to placebo, with several factors in favor of this finding.

First, UPLIFT was a very large trial, which more than doubles the size of the available safety database for Spiriva HandiHaler. There was a prespecified mortality analysis, with an independent committee to adjudicate cause of death and prespecified vital status collection. In addition, the finding persist across several

different analyses and a plausible mechanism, namely, reduction in COPD exacerbations, was demonstrated.

But since this is a major claim to even describe in the label, substantive evidence must be demonstrated. I would ask you to consider the strength of the evidence in your discussions this afternoon. Complicating any potential claim is the mortality imbalance in the Respimat trial, which we will now turn our attention to.

So far, we've reviewed only data from Spiriva HandiHaler, primarily from the UPLIFT trial, and have covered the exacerbation claim and potential safety signals of stroke and cardiovascular events. The remainder of the presentation will focus on Spiriva Respimat, with a discussion of the adverse mortality imbalance observed in one-year trials.

In contrast to the dry powdered formulation of tiotropium that's observed on the Spiriva HandiHaler, Spiriva Respimat is a solution formulated as an inhalational spray. It was tested

in Phase III trials in both 5 and 10 microgram doses.

The 5 microgram dose was approved in Europe, as you've heard, in 2007 and the European indication is a maintenance bronchodilator treatment to relieve symptoms in patients with COPD. We have here a picture of the Respimat device.

So I believe this slide will attempt to address some of Dr. Knoell's questions that he asked earlier. Comparing the systemic pharmacokinetics of the Respimat with the HandiHaler, here is a graph of the mean tiotropium plasma concentrations over time. So here's time and the plasma concentration on the Y axis.

The open triangles on the bottom are Spiriva HandiHaler 18 micrograms. The closed circles are Spiriva Respimat 5 micrograms, which are just slightly above, and substantially above, in the open circles, are Spiriva Respimat 10 micrograms. Note that this study is one of the trials in Caucasian that as mentioned by Dr. Disse.

The numbers look just slightly different in a study performed in Japan.

These PK data are consistent with the clinical adverse event profile from the Spiriva Respimat trial, which demonstrates increased systemic anticholinergic adverse events of dry mouth in patients receiving a 10 microgram dose compared to those who got the 5 microgram dose.

I'll also caution you that while the PK data between the Respimat 5 micrograms and the HandiHaler appear to be similar, the pharmacodynamic profile, as you heard from Dr. Chowdhury, of a locally acting product may not be comparable, given the fact that there are different aerodynamic particle size distributions, flow characteristics and lung deposition.

Thus far, there have been three one-year Spiriva Respimat trials in COPD patients showing a mortality imbalance in favor of placebo. All three trials were large, multinational studies. Trial numbers 205.254 and 205.255 were identically designed trials with three parallel treatment

groups -- Spiriva Respimat 5 micrograms, Spiriva Respimat 10 micrograms, and placebo.

The first primary endpoint for the trials was trough FEV1, with a planned pooling of data from the two trials for other endpoints, including COPD exacerbations. When the data were unblinded for these trials and a mortality imbalance was observed, Boehringer Ingelheim went back retrospectively and collected vital status data on patients who had discontinued from the trial to see if the imbalance could be explained by a healthy survivor effect in the placebo group occasioned by differential dropouts. Remarkably, the company was able to collect vital status and cause of death on 97 to 98 percent of patients in the trial.

The third trial, number 205.372, was a double blind, parallel group study comparing Spiriva Respimat 5 micrograms to placebo. This trial was designed primarily to look at COPD exacerbations. Vital status and cause of death were collected prospectively, similar to the fashion that you heard about for the UPLIFT trial.

The enrollment criteria for the Respimat trials were similar to those of the HandiHaler program and demographics were generally balanced across treatment groups.

I show here the combined demographics for all patients in the three Respimat trials that we're discussing. Overall, the demographics are remarkably similar to those in UPLIFT for Spiriva HandiHaler, with patients being predominantly white males, with a mean age of 65 and a baseline FEV1 of just over a liter.

The one difference that I would point out is here in Trial 372, where we have nearly 30 percent of the population being Asian. There were a number of sites in this trial in both India and China.

Turning our attention to Trials 205.254 and 205.255, bronchodilator efficacy was demonstrated, with both active treatment groups showing a significant improvement in trough FEV1 at 48 weeks of between 113 to 161 milliliters. While the 10 microgram group did show a larger treatment

effect in each study than the 5 microgram group, the difference between the active treatment groups was not statistically significant.

Now, looking at mortality in these trials, there was a small imbalance in favor of placebo in each trial. For Protocol 205.254, the numbers are seven in the Spiriva Respimat 5 microgram group and five in the placebo group. For Protocol 205.255, we have five deaths in the Respimat 5 microgram group compared to none in the placebo group.

While these numbers do look a bit better with inclusion of vital status, the imbalance does not go away completely and the percentages don't quite add up here, because they're calculated based on Kaplan-Meier estimates that adjust for censored observations in the denominator.

While the numbers for Spiriva Respimat are fairly consistent between the trials, the placebo numbers are quite variable. Given the patient population, it's extremely unusual to have no deaths in a group of patients followed for a

year.

Looking at cause of death in these trials, you can see that no particular pattern emerges and the numbers overall are small compared to what you saw in the HandiHaler trial. Myocardial infarction is slightly increased in the Respimat 5 microgram dose group, but there's no dose effect, so it kind of calls into question any conclusions that might be drawn from this result.

Looking at our third Respimat trial, number 372, both primary endpoints were met, with a significant improvement in trough FEV1, as well as an increase in the time to first COPD exacerbation. As you can see from this table, most of the secondary COPD exacerbation endpoints, including the proportion of patients with an exacerbation, the time to first exacerbation leading to hospitalization, and the number of exacerbations per patient year were also met.

Unfortunately, mortality was also increased in the Spiriva Respimat group, with a rate ratio ranging from 1.54 to 1.29, with

inclusion of vital status and 30-day follow-up data.

As you can see from an analysis of the cause of death, there is no particular signal that jumps out as driving the mortality imbalance. There were a few more lung cancer deaths in the Respimat group, but most of these occurred in the first 100 days of therapy, suggesting that they were a preexisting condition.

So to summarize, the Respimat data show a mortality imbalance in favor of placebo. The death rate in the Respimat group is not unexpected for the population, but the placebo rate is variable. There are no obvious other safety signals that could be linked to death in these studies.

As I pointed out previously, Spiriva Respimat is a completely different drug product from Spiriva HandiHaler that contains the same drug substance, tiotropium bromide. So the relevance of these data to Spiriva HandiHaler is unclear and I would leave it to the committee to consider during your deliberations.

Coming back to our outline, we've covered efficacy and safety data for Spiriva HandiHaler, along with pertinent mortality data from Spiriva Respimat. I will now bring us back to our objective for this session with some ideas to keep in mind for your discussion this afternoon.

Regulatory science is seldom black and white and this application is no exception. We've asked you to comment on the pros and cons of three different issues. First, do the data from the VA and UPLIFT trials provide substantial and convincing evidence that Spiriva HandiHaler reduces COPD exacerbations? While the data are supportive of the claim, you'll have to weigh this against the statistical issue of multiplicity due to failure of the primary endpoint in the UPLIFT trial.

Second, you're asked if the data from the UPLIFT trial adequately addresses the potential safety signals of stroke and cardiovascular events. On the one hand, you've got UPLIFT, which is the gold standard, randomized, placebo controlled, large trial with long duration of follow-up. On

the other hand, you've got these signals from pooled data and from meta analyses.

While the UPLIFT data do not suggest an increase in stroke or cardiovascular events, as I've pointed out, some of the confidence intervals, particularly for stroke, are rather wide.

Finally, you're asked to comment on the mortality in the UPLIFT trial, which showed a statistically significant mortality benefit in a large trial, with prespecified outcome measures for death. But complicating the issue are the three Respimat trials, with the mortality imbalance in favor of placebo.

So with that, I'll conclude the clinical portion of the presentation and turn the podium over to Dr. Joan Buenconsejo, the statistical reviewer for this application. Thank you for your attention.

DR. BUENCONSEJO: Thank you, Dr. Michele.

Good morning. I am Joan Buenconsejo and I'm a statistical reviewer supporting the Division of Pulmonary and Allergy Products.

The focus of my presentation is on the claim in the reduction of COPD exacerbation. I will also present results from both the UPLIFT study and the VA study. I will touch briefly on the mortality results from the UPLIFT study and the Respimat studies.

Dr. Lee had a slightly different view statistically on the claims in reduction of COPD exacerbation and on the mortality, and these are all presented in the briefing package. In this presentation, I am presenting my views.

The UPLIFT is a four-year study with almost 6,000 patients to compare the efficacy and safety of tiotropium versus placebo. The co-primary endpoints for the UPLIFT study are the yearly rates of decline in the pre and the post-bronchodilator FEV1 from day 30 to the end of double blind treatment. I will explain what co-primary means in this application later.

The primary analysis was conducted on all treated patients with at least three acceptable spirometric test sets. The goal was to compare the

yearly rates of decline in the pre and the post-FEV1 between the two treatment groups, and these are analyzed using a random effects model.

In the model, the pre and the post-bronchodilator FEV1 were assumed to follow linear trends over time. The intercept and slope were random coefficients and their covariance matrix were assumed to be unstructured. Several sensitivity analyses and subgroup analyses were performed for the primary endpoint.

The sponsor indicated two key secondary endpoints related to COPD exacerbation. These are the time to first COPD exacerbation and the time to first hospitalization due to COPD exacerbation. Both applied log rank tests and the hazard ratio was calculated using Cox regression.

The following is the multiplicity adjustment the applicant proposed in their statistical analysis plan prior to unblinding. First, the applicant proposed a sequential testing of the co-primary endpoints. The rate of decline in the pre-bronchodilator FEV1 is tested first at

0.049. If this is significant, then the rate of decline in the post-bronchodilator FEV1 is tested.

In parallel to this, the number of exacerbations leading to hospitalization will also be tested at 0.001. It is clear from this that the co-primary does not imply that the applicant has to win on both pre and post to get the claim of difference. Instead, this is done sequentially.

Now, for step two, if both co-primaries are significant, then sequential testing of key secondary endpoints is proposed, which is the time to first COPD exacerbation is tested first; then, if significant, then the time to first hospitalization is tested.

Now, the P values were adjusted due to interim analysis. There is no statistical significant difference in the yearly rate of decline in either the pre and the post-FEV1 between tiotropium and placebo.

The rates of decline for the two treatment groups are almost identical. Nonetheless, there is evidence of treatment

difference in the mean pre-bronchodilator FEV1 supporting the approved label claim. There is also evidence that the difference between treatment groups is maintained throughout the whole four years. That also supports the approved label claim.

Now, from a statistical standpoint, the primary endpoints did not win, and with a prespecified step-down approach, no secondary results can be considered statistically significant.

In the next two slides, I'm going to present the results from the analysis of COPD exacerbation. The risk of COPD exacerbation is 14 percent lower in the tiotropium arm than placebo. The median time to first exacerbation is about four months longer in the tiotropium-treated patients than in the placebo-treated patients. However, the proportion of patients with at least one COPD exacerbation is not different between the treatment groups over the four-year period.

The risk of hospitalization due to COPD

exacerbation is also 14 percent lower in the tiotropium arm than in the placebo arm. Hospitalization also occurred sooner in the placebo-treated patients than in the tiotropium-treated patients.

I am now going to shift focus and give a brief background on the VA study. The VA study is a six-month study of close to 2,000 COPD patients. The co-primary endpoints for this study are the proportion of patients experiencing a COPD exacerbation during the six-month treatment period and the proportion of patients hospitalized for an exacerbation during the six-month treatment period.

The goal was to compare whether there is a treatment difference in these primary endpoints using the Cochran-Mantel-Haenszel test, with center as the stratifying variable.

The sponsor indicated several secondary endpoints related to COPD exacerbation. This includes time to first COPD exacerbation and time to first hospitalization. Both applied log rank tests and the hazard ratio is calculated using Cox

regression. Of note, the analysis of time to first COPD exacerbation is of particular interest in this submission if the sponsor is proposing this claim in the label.

The following is the multiplicity adjustment the applicant proposed in their statistical analysis plan. Similar to the UPLIFT study, sequential testing of the co-primary endpoint is proposed. The proportion of patients experiencing a COPD exacerbation during six months' treatment period is tested first; then if this is significant, then the proportion of patients hospitalized will be tested at 0.05.

No multiplicity adjustment was mentioned for the secondary endpoints, like the time to event endpoints. The percent of patients with a COPD exacerbation was statistically significantly lower for tiotropium compared to placebo. The proportion of patients hospitalized for exacerbation was not a statistically significant difference between tiotropium and the placebo.

Kaplan-Meier plots associated with each

of the primary efficacy endpoints are given in the next two slides. The risk of COPD exacerbation is lower in the tiotropium arm than in the placebo arm. Exacerbation occurred sooner in the placebo-treated patients than in the tiotropium-treated patients. Similarly, the risk of hospitalization is also lower in the tiotropium arm than in the placebo. Hospitalization due to exacerbation occurred sooner in the placebo-treated patients than in the tiotropium-treated patients.

In summary, there is evidence from the VA study that the odds of a COPD exacerbation are reduced by tiotropium relative to placebo. However, we can't ignore the fact that the prespecified co-primary endpoints did not win and that multiplicity adjustment procedure was prespecified. That approach the applicant chose does not allow one to make statistical inference at the secondary endpoints when primary endpoints did not win.

Now, I'm going to switch gears and discuss mortality. Like COPD exacerbation,

mortality is classified as a secondary endpoint. However, unlike COPD exacerbation, mortality can be considered as a primary endpoint if analyzed properly and supported by other studies.

D'Agostino, O'Neill and others argue that the usual reason for designating mortality as a secondary endpoint is that the trialist believes a priori that there is little chance a treatment spec will be observed given the sample size and the power to detect an effect on mortality. But if this is observed, statistically significant findings of mortality is important.

In the UPLIFT study, there is some suggestion of a benefit of tiotropium on treatment mortality. In general, the hazard ratio is about 0.85, with a confidence interval lying entirely below the norm. The survival curve for the tiotropium arm is above the placebo.

Because a different result was observed in another Spiriva application using the Respimat delivery system, the result from the UPLIFT needs to be explored further. Of note, in the Respimat

application, more deaths were observed in the Spiriva Respimat treatment groups compared to placebo in a one-year trial.

In summary, there is some suggestion of a benefit of tiotropium using the HandiHaler system on treatment mortality. However, a different result was observed when the Respimat delivery system is used.

Thank you for your attention. Dr. Simone Pinheiro from the Office of Surveillance and Epidemiology is going to present her findings.

DR. PINHEIRO: Good morning. My name is Simone Pinheiro and I am an epidemiologist at the Division of Epidemiology in the Office of Surveillance and Epidemiology. Today, I will present a review of the safety evidence concerning tiotropium bromide from an epidemiology perspective.

In this presentation, I will first describe the published evidence that raised questions regarding the safety of tiotropium bromide. I will then present an evaluation of the

strength of this evidence, particularly in light of UPLIFT, a four-year placebo controlled trial previously discussed both by the applicant and more recently by Drs. Michele and Buenconsejo.

Following, I will present a brief summary of findings of other studies. These include meta analysis of randomized trials that have been published in the literature and observational studies.

I will then conclude with a few slides to summarize the main point of this presentation. Please note that data from unpublished tiotropium Respimat trials will not be discussed in my presentation.

The safety of tiotropium bromide was recently questioned in a meta analysis of randomized clinical trials published in the Journal of the American Medical Association on September 24th of 2008. This meta analysis, which included 17 trials, of which 12 were tiotropium trials, suggested that use of tiotropium may be associated with a 43 percent increased risk of cardiovascular

events, which included nonfatal stroke, nonfatal myocardial infarction, and cardiovascular deaths.

The confidence intervals around these estimates overlapped the null value of 1, which means that one cannot be certain of the direction of the risk. This meta analysis also suggested that use of anticholinergics, including tiotropium and ipratropium, was associated with a near 60 percent increase in risk of cardiovascular events compared to control.

The confidence intervals about this estimate did not include the null value of 1. Additionally, inhaled anticholinergic use was also associated with a near 30 percent increase in risk of all cause mortality in this meta analysis. The confidence intervals about this estimate overlap the null value of 1.

Please note that on this slide and throughout my presentation, I will denote point estimates for which the corresponding confidence interval does not include the value of 1 in bold.

Within two weeks of this publication, on

October 9th of 2008, the results of a four-year placebo controlled, randomized clinical trial named UPLIFT were published in the New England Journal of Medicine. This trial has been discussed today both by the applicant and by Drs. Michele and Buenconsejo.

In contrast with the meta analysis published in JAMA, this large, long-term, randomized clinical trial suggests that tiotropium may be associated with a 16 percent decreasing risk of cardiac events. These included terms such as angina, atrial fibrillation, cardiac failure, congestive heart failure, coronary artery disease, and myocardial infarction; also, with a 13 percent decreasing risk of all cause mortality compared to placebo. The confidence intervals about these estimates did not include the null value of 1.

I will now briefly describe the meta analysis published in JAMA, which raised concerns regarding the cardiovascular safety of tiotropium. The main objective of this meta analysis was to evaluate the risk of cardiovascular events

associated with use of inhaled anticholinergics in COPD randomized clinical trials.

Studies were included in the meta analysis if they met the following inclusion criteria: if they were randomized trials lasted more than 30 days; if they are trials of COPD patients; if they compared anticholinergics against active controls or placebo; and, if they reported data on incidence of serious cardiovascular events.

The primary outcome of this meta analysis is a composite of nonfatal stroke, nonfatal myocardial infarction, and cardiovascular deaths. The secondary outcome of this meta analysis was all cause mortality. Risk ratios for each individual trial were pooled using fixed effect models in the main analysis.

A total of 103 trials were then reviewed in detail. Of these, 86 trials were excluded for the following reasons: 15 because they were not randomized trials comparing anticholinergics against controls that lasted more than 30 days; 69 because they did not report on cardiovascular

events; and two because they lacked events on both study arms; leaving 17 randomized clinical trials for these meta analyses, 12 of which were tiotropium randomized clinical trials that included over 8,000 patients.

Subsequently, it was noted that two of these trials had been captured by earlier publications, resulting in double counting of participants. Additionally, the number of controls in one of the trials was less than what was reported in the meta analysis published in JAMA.

A corrected meta analysis was published in the March issue of JAMA, of this year. It included 10 tiotropium randomized clinical trials, displayed on this table. In this second column, from left to right, I show the types of controls used in each of these randomized trials. You'll notice that seven of these trials are placebo controlled trials and three of them were active control trials. Active controls included either placebo and salmeterol or a combination of salmeterol and fluticasone.

The third column from left to right shows the duration of each of these trials and you'll notice that only four of the trials lasted more than six months.

The very last column to your right shows you the risk ratios of cardiovascular events for each of the trials. These ratios range from 0.3 to 3.3, with wide confidence intervals.

The corrected meta analysis suggests that tiotropium was associated with a near 50 percent increase in cardiovascular events compared to controls. The confidence interval about this estimate included the no value of 1.

This increase in risk in cardiovascular events was restricted to trials of long duration, defined by the investigators of this meta analysis as those lasting longer than six months.

Among the long-term trials, among which follow-up ranged from 42 to 104 weeks, tiotropium use was associated with a near twofold increase in risk of cardiovascular events. Combined, these long-term trials included approximately 3,000

patients. Among short-term trials, the risk ratio of cardiovascular events was 0.9, with confidence intervals that overlapped the null value of 1.

Analysis combining both tiotropium and ipratropium randomized trials suggested that use of these products may be associated with a 60 percent increase in risk of cardiovascular events. This increase in risk was mostly driven by increase in risk of myocardial infarction and cardiovascular death.

The risk ratio for stroke was 1.5, with confidence intervals overlapping 1. This analysis also suggested that anticholinergics may increase the risk of all cause mortality by 30 percent compared to control, although the confidence intervals included the null value of 1.

I'll now discuss the strength of the evidence provided by this meta analysis published in JAMA and contrast it against the evidence provided by UPLIFT, particularly as it relates to the relevant safety outcomes.

I'll focus my discussion on six potential

limitations of the meta analysis published in JAMA. Most of these stem from the fact that meta analysis typically rely on reported data. These limitations include potential biased selection of studies, inability to properly account for imbalance in follow-up, potential for informative censoring, potential for confounding, incomplete outcome information, and combining of study drugs.

A discussion of each of these limitations and their potential implications will follow over the next few slides.

The first limitation refers to a potential biased selection of studies. Approximately two-thirds of the considered studies were not included in the meta analyses because they failed to report on cardiovascular adverse events. However, publication of trials are typically summary reports. Studies without an imbalance in cardiovascular adverse events may be also less likely to report on these events.

Therefore, the increase in risk in cardiovascular events reported in the meta analysis

may be due, at least in part, by a selection of a non-random subset of studies, where an imbalance in safety outcomes would have been observed.

The second limitation refers to inability to properly account for imbalance in follow-up time. Overall, discontinuation rates were higher among placebo compared to tiotropium-assigned participants. Shown here are the overall discontinuation rates for the trials comparing tiotropium against placebo.

Due to the higher discontinuation amongst placebo participants, person time data would more properly account for exposure to medication. However, person time data was not considered in the meta analysis.

The third limitation refers to a potential for informative censoring. It has been suggested that participants on an inferior treatment, such as placebo, may be more likely to discontinue participation due to deterioration of health status. Therefore, placebo participants who remain on the trial may be, in general, healthier

than participants in the tiotropium arm.

The fourth limitation refers to a potential for confounding. Trial discontinuation may result in an imbalance of both known and unknown confounders between participants who remain on the trial. Analysis has stratified the predictors of cardiovascular adverse events, including, but not limited to, current smoking status and concurrent use of cardiac medications, would have been informative, but were not pursued.

Fifth, outcome data is likely to have been incomplete as information on adverse events and vital status was not collected for participants who discontinued trial in at least 50 percent of the included studies.

Finally, the main analysis of the meta analysis published in JAMA combines two different study drugs, tiotropium and ipratropium. The long versus short-acting nature of these products may have different implications for systemic effects, such as cardiovascular events. Therefore, summary estimates over tiotropium and ipratropium trials

are difficult to interpret.

I will now briefly discuss the findings of UPLIFT that concern the relevant safety issues raised by the meta analysis published in JAMA. This randomized trial has been discussed today in greater detail by both the applicant and by Drs. Michele and Buenconsejo. Briefly, UPLIFT is a multicenter, multinational, randomized clinical trial that compared four years of therapy with either tiotropium or placebo in COPD patients. This trial included approximately 6,000 patients.

Safety endpoints included all adverse events, including serious adverse events and all cause mortality. The vital status was collected on all patients, including those who prematurely discontinued trial and was known for 97 to 98 percent of the patients. The primary cause of death was adjudicated by an independent committee.

This table shows the main results of UPLIFT related to cardiovascular adverse events. Contrary to the meta analysis published in JAMA, findings from UPLIFT did not suggest an increase in

risk of cardiovascular events with use of tiotropium.

A total of 672 participants developed cardiac events, including angina, atrial fibrillation, cardiac failure, congestive heart failure, coronary artery disease, and myocardial infarction. The incidence rate ratio of cardiac events comparing tiotropium against placebo was 0.84, with confidence intervals that did not include the null value of 1. The rates of stroke were similar between tiotropium and placebo participants, but the estimate was imprecise and the upper bounds of the confidence limits reached 1.3.

The rate ratio for cardiovascular events, including myocardial infarction, stroke, and cardiovascular deaths, which included the MedDRA preferred terms of sudden death, sudden cardiac death and death of unknown cause, therefore, approximating what was used in the meta analysis published in JAMA, was 0.81, with confidence intervals that did not include the null value of 1.

This next table shows the main results of UPLIFT that concern mortality. The first row shows results for adjudicated deaths while on treatment. The second and third rows show results for adjudicated deaths, including post randomization, discontinuation, and vital status, with a cutoff date of four years or four years plus 30 days.

Overall, the total number of deaths during treatment, which included the last day of study drug plus 30 days, was 792. The hazard ratio for all cause mortality was 0.84. The confidence interval for this estimate ranged from 0.73 to 0.79.

Compared to on-treatment mortality, an additional 149 deaths were identified for patients that discontinued the trial. The mortality findings are robust and death risk was significantly lower or close to significantly lower in patients treated with tiotropium compared to placebo, regardless of the cutoff they used or the inclusion of vital status data after discontinuation.

The most common causes of adjudicated deaths on treatment were COPD exacerbations, lung cancer, and death of unknown cause. Therefore, in general, the findings of UPLIFT did not agree with the findings of the meta analyses published in JAMA and they did not suggest an increase in risk of cardiovascular events or mortality. However, some of the estimates are imprecise, including those for stroke. Due to limitations of the meta analysis, UPLIFT may provide stronger evidence regarding the safety of tiotropium.

I will next briefly summarize the findings of other meta analysis of randomized clinical trials that have been published in the literature. I will also briefly summarize the findings of observational studies conducted to evaluate the safety of tiotropium.

Six other meta analyses of tiotropium randomized clinical trials were identified in the published literature. These meta analyses included from 3,600 to close to 20,000 patients. Several trials overlapped across these meta analyses. Two

of these analyses included UPLIFT. Two of these meta analyses considered person time data, and one meta analysis examined the risk of cardiovascular events according to trial duration. However, contrary to the meta analysis published in JAMA, tiotropium was not associated with increase in risk of cardiovascular events regardless of the duration of the trial.

The main limitations of these meta analyses include the fact that cardiovascular events were not the primary endpoint in most of the included trials.

This table shows the range of relative risks for relevant cardiac events and mortality comparing tiotropium and control, reported by the aforementioned meta analyses. This column here shows a number of the analyses that examined each of the endpoints. This column here shows the lowest point estimates, along with their corresponding confidence intervals. This column shows the highest point estimate, along with its corresponding confidence interval.

The point estimates for myocardial infarction ranged from 0.7 to 0.1. For cardiac failure, point estimated ranged from 0.6 to 0.8. For stroke, they ranged from 1.0 to 1.1. Point estimates for all cause mortality ranged from 0.8 to 0.9. Cardiovascular related mortality, these estimates ranged from 0.6 to 1.2. For respiratory related mortality, these estimates ranged from 0.5 to 0.8.

Please note that most of these confidence intervals do include the null value of 1 and some of the estimates are rather wide.

Several observational studies also examined the safety of tiotropium and were identified in the literature. These include three published population-based cohort studies, a cohort study conducted in a Danish house care registry that included over 10,000 COPD patients, a study conducted in the U.K. THIN database that included close to 3,000 patients, and a Canadian study using the Canadian Institute of Health information hospital discharge database that included over

7,000 patients.

Additionally, an unpublished case-control study in a cohort of about 6,800 COPD patients in the integrated primary care information database in the Netherlands is also included in this review. This study was submitted to us by the sponsor.

One of these studies compared tiotropium use versus non-use, one study compared use of tiotropium, current use of tiotropium against no use of anticholinergics, and three of these studies compared the use of tiotropium against use of LABA.

The main limitation of these studies was the fact that most were unable to properly adjust for potential important confounders, including smoking, BMI, disease severity, and lung function. Additionally, insufficient power may be an issue in at least one of these studies.

This table summarizes the range of relative risks concerning relevant endpoints observed in these observational studies. The lowest and highest point estimates for each outcome are displayed in this table in these columns.

Corresponding confidence intervals are shown within parentheses.

The relative risk of myocardial infarction ranged from 0.8 to 1.3. For cardiac failure, it ranged from 0.7 to 1.3. Only one study reported on stroke, risk of stroke, and the point estimate was 0.9. The point estimates for all cause mortality ranged from 0.8 to 0.9.

Mortality related to specific cardiac events was reported in one study. The lowest estimate displayed here refers to the relative risk of sudden death and the highest relative risk shown here refers to mortality related to myocardial infarction. Only one study reported estimates for respiratory mortality; the relative risk was 0.8. It's important to note that these estimates are generally imprecise and overlapping the null value of 1.

In summary, similarly to the findings of UPLIFT, all the meta analyses of randomized clinical trials didn't seem to suggest an association between tiotropium and increased risk

of cardiovascular events or mortality. However, confidence limits overlapped the null value of 1 and many of them were wide.

Additionally, most of the observational data did not indicate an association between tiotropium and increased risk of cardiovascular events or mortality. However, most estimates are, again, imprecise and many include the null value of 1.

I'll conclude this presentation with a few summary slides. In summary, the data regarding safety of tiotropium are rather complex. Findings from a meta analysis of randomized trials published in JAMA suggest an increase in risk of cardiovascular events, particularly among trials of long duration, as well as an increase in mortality in the tiotropium group compared to control.

Data from three Respimat trials, not discussed in this presentation, but addressed in the previous presentations today, suggested a numerical imbalance in mortality that favored placebo.

On the other hand, UPLIFT did not suggest an increase in risk of cardiovascular events. It suggested a decrease in risk of death. UPLIFT is the largest and longest tiotropium trial. Mortality endpoints were prespecified and vital status was collected and adjudicated for all participants, including those who prematurely discontinued trial.

Mortality results were robust against different analyses. However, note that the primary endpoints of this trial related to lung function. Also, estimates for stroke were imprecise and the upper bounds of the confidence limits reached 1.29.

Six other meta analyses of tiotropium randomized clinical trials were identified in the literature. In general, the findings are consistent with results from UPLIFT in that they did not suggest an increase in risk of cardiovascular events or mortality. However, most confidence intervals reported in these meta analyses overlapped the null value of 1.

Additionally, most of the observational

data also didn't seem to suggest an association between tiotropium and increased risk of cardiovascular events or mortality. However, the reported estimates were rather imprecise and most confidence intervals overlapped the no value of 1.

Thank you for your attention.

DR. BRANTLY: Thank you very much. I'd like to invite the committee members to now present questions to the FDA evaluation team.

Dr. Hendeles?

DR. HENDELES: My question is I just want to confirm what I heard that there was no dose response relationship for adverse effects in the Respimat data.

DR. MICHELE: That's actually not correct. There was a dose response for some adverse events, most notably, dry mouth, which was increased in the 10 microgram group compared to the 5 microgram group.

DR. HENDELES: But not in serious adverse events, such as cardiovascular.

DR. MICHELE: No. There was no increase

in that.

DR. BRANTLY: Dr. Platts-Mills?

DR. PLATTS-MILLS: In the efficacy data, it appears that there is no effect in the patients who are current smokers and there's a different prevalence of current smoking in the UPLIFT study, which is 29 percent, compared to the Respimat studies that are 36 percent.

Is that relevant? Do we actually have separate data showing that the bronchodilator effects of tiotropium are the same in current smokers and non-smokers?

DR. MICHELE: So if I could summarize that, you're asking me to compare the data from Respimat with regard to efficacy, and, in particular, the subgroup analyses for smokers, to the data from HandiHaler for efficacy for exacerbations; is that correct?

DR. PLATTS-MILLS: I recognize that might be more fairly a question for them.

DR. MICHELE: It might be. I would just throw out a caution, though. By our viewpoint, we

don't believe that those two datasets are directly comparable, because Respimat is a different drug product and, as we've noted, they're locally acting.

What I did with my presentation was I just wanted to provide a balanced viewpoint so that you weren't looking just at mortality data from the Respimat.

I'll now turn it over to Dr. Kesten for a comment on that.

DR. PLATTS-MILLS: Could I ask another specific question? Do we know why Respimat was not approved at 10 micrograms in Europe? That is, the trials were done with 10 micrograms and 5 micrograms, but as far as I understand, it was only approved at 5 micrograms.

DR. MICHELE: Again, Dr. Kesten may wish to answer that with regard to what you requested for approval.

DR. KESTEN: I'd like to, if I may, address both the questions.

Could I have the slide with the subgroup

from UPLIFT with baseline smokers and ex-smokers? Because the question was exacerbations based on baseline smoking behavior.

While I'm waiting for that slide, I'll address the other question. We requested approval of Respimat 5 micrograms as we saw similar efficacy and more inhaled anticholinergic-related effects, such as dry mouth is related, and it was approved at the 5 microgram formulation.

Slide up, please. So with regard to your question of baseline smoking behavior, this is people who -- I'm sorry. There's a lot of lines there, but if you go to the third category of smoking, this is based on self-report of saying, "Yes, I'm a current smoker" or "I'm an ex-smoker. I no longer smoke." And the hazard ratios are for the risk of an exacerbation and it's 0.86 versus 0.85, so very similar effects according to baseline smoking behavior.

DR. BRANTLY: Another question?

DR. TERRY: I wanted to ask the FDA representatives how important they think it is that

the secondary analyses, endpoint analyses, be predicated on a successful analysis of the primary endpoints?

DR. CHOWDHURY: That's a question that actually we are asking you to comment on.

[Laughter.]

DR. CHOWDHURY: I will turn it back and we'll discuss this during the discussion period.

DR. TERRY: Well, I just wanted to know. It's not in the discussion period, though. The questions in the discussion period don't actually include this. So can it be discussed now or can we discuss it during the discussion period, even though it isn't actually a topic of discussion?

DR. CHOWDHURY: I suggest we keep it for the discussion period.

DR. TERRY: Okay. We can talk about that.

DR. CHOWDHURY: We can talk about that at the discussion period.

DR. TERRY: Great.

DR. BRANTLY: Dr. Schoenfeld, do you have any other comments regarding the meta analysis and the UPLIFT trial?

DR. SCHOENFELD: I have no questions. This is the question period. I have no questions relative to the meta analysis or what was presented. But I'll comment on what you just commented on in the discussion period.

DR. BRANTLY: Dr. Newman?

DR. NEWMAN: I guess this question is for Dr. Michele, and maybe Dr. Kesten will need to comment on this, as well.

In terms of trying to reconcile the mortality differences, Dr. Kesten speculated that the numerical imbalance in deaths could conceivably be related to withdrawal, a differential withdrawal of severe COPD patients from placebo groups between the Respimat and the UPLIFT.

I'm just wondering if you have any comment or observation on that. You showed us some of the demographics, but the Gold criteria perhaps for the Respimat as compared to the UPLIFT might be

interesting to understand. Was there, in fact, a differential withdrawal, and if you modeled it, would it make a difference?

DR. MICHELE: We were actually concerned about that point, as well, when we saw the initial data on 205.254 and .255. So that had a lot to do with why the company went back retrospectively and collected vital status data.

So when you add in the vital status data, you can see that at least a portion of that mortality imbalance was explained by differential dropout, because it gets better, but it doesn't go away.

So then you're left with, okay, now what does it mean. And I think, again, this is a topic of discussion for the committee. But I'll throw it open to Dr. Kesten and see if you have further comments on that.

DR. KESTEN: Thank you, Dr. Michele, for allowing an opportunity to address that, because it is one of the important issues today.

We have some very experienced people in

epidemiology and particularly in the cardiovascular area and I'd ask, if I may, Dr. Hennekens, with his wealth of experience, to comment on the issue that's raised.

DR. HENNEKENS: My name is Charlie Hennekens. I'm the Sir Richard Doll Research professor at Florida Atlantic University. Today is the third occasion on which I've been asked to give my independent scientific views to Boehringer Ingelheim and for which I receive compensation for travel expenses and honoraria. I've had no other involvement with Boehringer Ingelheim since 1999, when I participated with them an FDA Advisory Committee meeting for Aggrenox.

I think it's also important to disclose that on December 4, 2009, with my coauthor, Dave DeMets, I published a manuscript in JAMA entitled "The Need for Large-Scale Randomized Evidence Without Undue Reliance on the Results of Small Trials, Their Meta Analyses, or Subgroup Analyses."

So with respect to total mortality, the large-scale randomized evidence derives from UPLIFT

and has about 915 deaths. The total number of deaths from the six small trials of Respimat has about 146. The UPLIFT gets divided about 430 in tiotropium and 491 in placebo, a relative risk reduction of about 17 percent, with 95 percent confidence intervals from 0.66 to 0.99.

If one looks at all the Respimat deaths, there are 85 versus 61, about, so that the totality of evidence is 515 versus 552, a possible, but non-significant seven percent reduction, but 95 percent confidence interval that suggests a possible benefit as big as about a quarter and a hazard about -- reassuring hazard no greater than about 10 percent.

In addition, as Dr. Pinheiro pointed out, the observational studies did not really suggest any signal for any increasing mortality, although subject to the limitations of uncontrolled and uncontrollable confounding, which is about as big as the effect size that's being sought in the randomized evidence.

I do take Dr. Suissa's point that if

there were confounding by indication in the observational studies, then one would speculate that sicker patients might be more likely treated, but this is just speculation.

My own conclusion is that Dr. Michele's and Dr. Pinheiro's outstanding presentations were largely consonant. I find her proposed hypothesis about decrease in total deaths from exacerbations to provide a plausible mechanism for the observed decrease in mortality in UPLIFT to be insightful and intriguing and, also, unusual that that is proposed by the FDA, not the sponsor.

However, my own independent scientific view of the totality of evidence is that the evidence is very reassuring against any increased risk of totally mortality, although I am somewhat less certain that there is a decrease in total mortality.

Finally, I concur with Dr. Buenconsejo's cogent argument about how to deal with total mortality as a secondary endpoint with FEV as a primary endpoint. Indeed, however, I would extend

this very same cogent argument to exacerbations in FEV1.

This is because my own personal view is that these hierarchical models are important for the analyses of primary and secondary endpoints when the secondary endpoints really are dependent upon the primary, which would be the case, say, in a combined endpoint of all cardiovascular events, nonfatal, and nonfatal stroke and vascular deaths, where you find nothing and then propose that there is a benefit or harm due to one component of it. But here, these are largely independent.

So I think that really summarizes my views on the issue. Thank you very much.

DR. BRANTLY: Dr. Newman?

DR. NEWMAN: Excuse me, before you leave. Thank you for your comments. But could I ask you what part of your answer answered my question?

DR. HENNEKENS: I believe that you asked me to comment on the total mortality issue.

DR. NEWMAN: I was trying to reconcile the speculation by Dr. Kesten that the potential

trial-related contributing factors may have been with the differential withdrawal of the most severe COPD cases in the placebo group of one set of studies versus the other.

DR. HENNEKENS: Well, I'm sorry, I misunderstood your question. Then I'll ask Dr. Kesten to respond.

DR. KESTEN: I'd like to actually directly respond to your question. When we look at the discontinued patients, they are clearly more severe. If you look at the Gold Stage and some of the co-morbidities, you see a higher load of disease there, and they do preferentially drop out of the placebo group.

Now, even with the vital status collection, it becomes very complicated, particularly in the Respimat trials, where there was widespread availability of tiotropium, which wasn't necessarily the case when we started the UPLIFT trial. So patients could decide, and their physicians, to drop out, go on an active product, which is actually in the trial. So I can't tell

you definitively. I think there are confounding factors here that need to be considered, and I hope that answers your question.

DR. NEWMAN: Thanks.

DR. BRANTLY: Dr. Platts-Mills?

DR. PLATTS-MILLS: I apologize. My previous question was phrased wrongly. I really wanted to look at Dr. Michele's slide number 34. First, before that, I'd like to thank Dr. Michele for her presentation, which I enjoyed a lot.

In that 34, it's the mortality in UPLIFT, where there was no effect in the current smokers. The question is, is that also true -- is there a difference between current smokers and former smokers in the other studies, where there's mortality?

DR. MICHELE: If I could address that. From the Respimat trials, I don't have a subgroup analysis on mortality to show you, because they were small numbers. In this one, I would note that the former smoker group is about twice as big as the current smoker group. So it's only about a

third of patients that were current smokers. So whether that has anything to do with the wider confidence intervals in the current smokers, I'm not sure, but it may be a contributing factor.

DR. PLATTS-MILLS: But given the change in the status of smoking, that it is now an FDA issue, this is clearly a drug interaction that we need to --

DR. MICHELE: I'm all for banning cigarettes.

DR. BRANTLY: Dr. Wolfe?

DR. WOLFE: If you combine 254 and 255 and look at the deaths in three roughly comparable groups in terms of their size, you have five in the placebo, 12 in the 5 micrograms and 16 in the 10. So in addition to the anticholinergic dryness and so forth, there is some suggestion of an increased dose response adverse effect in this case.

I go back to the statement by the company this morning that there was roughly, in terms of the delivered amount of the drug, about 1.3 times higher with the Respimat than the other. So I'm

just putting forth an alternative hypothesis instead of just that there is some dropout of the placebo. There's actually a higher dose of something and there was, in fact, some at least suggestion -- the numbers are small, as Dr. Hennekens pointed out, but at least it's trending in the direction of 5 placebo -- 12 to the 5 and 16 deaths is the total deaths.

So I don't see how one can dismiss the dose response possibility as in Respimat is delivering more drug than the version we're talking about. I agree with the statements that in terms of efficacy, that's not something -- it's good to see the information, but it's not something that we want to talk about. IIn terms of safety, it is the same drug and if we're getting more of it in one, that may be some insight into the fact that it's more dangerous.

DR. HONSINGER: The one bit of data that we have not seen is any compliance data. I don't know if either the FDA or the sponsor has compliance data. There must have been something in

the way of compliance. If it was a pill that can be used once a day, you must be counting pills or something.

I certainly think that patients are likely to take their medicines when they're having symptoms. They're likely to take their medicines on the day that they're having their appointment for their pulmonary function test. When it comes to the analysis of this drug, if somebody should advise that it be taken, should it be taken with symptoms or should it be taken all the time? Do we have any compliance data?

DR. MICHELE: I believe that Dr. Kesten addressed that point earlier. In the UPLIFT trial, they did do pill counts for pierced capsules. The compliance data did go down over time, but overall, in the study, it was fairly good. I believe he mentioned 90 percent at one year and 80 percent at four years, and those data are available in the background package in my review, the exact numbers.

DR. BRANTLY: Any further questions from the committee members? Dr. Newman?

DR. NEWMAN: I have one for the FDA and I'm not sure who should answer this, but it's sort of a broader question. In the major studies that have been done, the researchers have been careful to exclude people with various kinds of cardiovascular risks and I understand why that is.

How might I reconcile that with the labeling and instructions regarding Spiriva, which, as best I can tell, when you look at things like contraindications, warnings and precautions, it doesn't really say you shouldn't take this if you have cardiovascular risk?

DR. MICHELE: So if you'll note that the warnings and precautions that are in the label for Spiriva HandiHaler, those patients were consistently excluded; that is, patients with narrow-angled glaucoma and patients with known urinary retention and prostatic hypertrophy and so forth.

As far as Phase III trials, in general, there are a lot of exclusions that don't necessarily mean that the drug should never be used

in those patient populations. I would point out that in UPLIFT, as well as the VA trial, the exclusion criteria were significantly more liberal with regard to myocardial infarction and other cardiovascular events at baseline compared to the Phase III trials that were run for Spiriva HandiHaler.

I'll ask if Dr. Chowdhury has further comments on that.

DR. CHOWDHURY: I don't have much to add here, but just to point out that it is very true, when the early studies are done, usually pre-registration studies or studies for early development, we have these restrictions on entry criteria because the drug is not really very, very well characterized.

For that reason, actually, we depend on post-marketing when the drug is approved and has very frequent monitoring of the post-marketing report to pick up adverse effects if they come up, and depending on the registration criteria, as well, and what the findings were when they do the

post-marketing studies.

So what you're asking is a very valid question. Some of the real life studies, that actually happens very often after marketing.

But I'll ask if Dr. Iyasu has any comment on this or not.

DR. IYASU: I don't think I have any additional comments, but it's an important consideration in the balance of evidence that one has to consider pre-approval versus post-approval. I think we're looking forward to your advice on how you balance out that evidence base, pre-approval versus approval.

But I think in this case, we are faced with a situation where we have interesting information that needs some interpretation from your side as to how to go forward with it. But it all boils down to what is the right balance that one has to have. So it's a very global question that you are asking and it's a pertinent one.

DR. BRANTLY: Dr. Platts-Mills?

DR. PLATTS-MILLS: I've got a point and a

question. First of all, I love the idea of excluding cardiovascular risk in 65-year-old men.

[Laughter.]

DR. PLATTS-MILLS: On the compliance issue, the two major risk factors -- on the compliance issue, in asthma, they have reached the point where you actually have timers on the inhalers so that you can actually tell at what time the thing was compressed.

With the pierced capsules, is it easy to pierce a capsule and so repeatedly pierce some capsules without taking the inhaler, or is it really almost inevitable that if someone pierces a capsule, they've actually taken the drug?

DR. KESTEN: Dr. Platts-Mills' question is related to the compliance issue. So what we did, as I said, is the patient puts the capsule in the device, pierces it, administers the medication, and we ask them to keep their medication, bring it to the clinic.

I certainly can't rule out the possibility that someone would go to the effort of

putting it in, piercing it, not taking it, and almost in a dose-dumping fashion that led to some of the studies we were referring to in asthma. Certainly, I can't rule out that possibility.

But what I would say is that if people were doing that and having reduced compliance, that would, if anything, work against showing the effects that we're seeing on lung function and exacerbations.

DR. BRANTLY: Dr. Hendeles, do you have a question?

I think that, at this point, we'll break for lunchtime. We'll be back at 1:00 on the dot. I remind the committee members to withhold from any discussions regarding the topic at hand.

(Whereupon, at 12:07 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

DR. BRANTLY: We'll get started now. As promised, I wanted to start on the dot. It is now 1:00. We have no one scheduled for the open public

hearing, therefore, we will go directly to Dr. Seymour's talk.

Are there any individuals in the audience that would like to speak?

Not hearing anybody volunteer, Dr. Seymour, thank you very much.

DR. SEYMOUR: Good afternoon. My name is Sally Seymour. I'm the Deputy Director for Safety in the Division of Pulmonary and Allergy Products. I just want to reassure you that I don't have a presentation really. This is just an introduction to the questions.

At this point in the meeting, we've heard the presentations from both the FDA and the sponsors, and I just want to present the questions that we pose for the committee to discuss. These questions really relate to the objectives for today's meeting, which were to discuss the HandiHaler efficacy information regarding the reduction of exacerbations in patients with COPD. Also, we've talked a lot about safety signals related to stroke, MI, cardiovascular mortality,

and all cause mortality.

So with that in mind, we actually have five questions, two of which are discussion questions and three are voting questions. But I do want to remind you that you can certainly take time before the voting questions to have a discussion on the topic before you vote on it to make sure that all your comments are heard. Those are important to us.

So the first question for discussion is please comment on the mortality data from the Spiriva HandiHaler trial for UPLIFT. I think what we're interested in here in this question is really the strengths and weaknesses of the data that you've seen today.

This is a similar question. You've seen some mortality data for the Spiriva Respimat Phase III trial and we'd like you to comment on the mortality data that you've seen; again, information along the lines of what you see are the strengths and weaknesses of this information.

The first voting question is regarding

the COPD exacerbation claim, and let me read it.

Do the data from Trials 205.235, UPLIFT, and 205.266, the VA study, provide substantial and convincing evidence to support the claim that Spiriva HandiHaler reduces COPD exacerbations and if not, what additional data are needed? We certainly encourage you to discuss the efficacy data before you decide to vote on this question.

The next voting question has to do with the stroke issue. Do the data from Trial 205.235, UPLIFT, adequately address the potential safety signal of stroke events and if not, what additional data are needed? And, again, we would encourage discussion about the strength of the information regarding the stroke signal and the weaknesses of that information, as well.

Then, finally, the last voting question; do the data from Trial 205.235, UPLIFT, adequately address the potential safety signals of adverse cardiovascular outcomes, and if not, what additional data are needed?

We look forward to your discussions and

thank you very much.

DR. BRANTLY: Okay. We'd like to begin the discussion portion. First, I'd just like to remind the committee of a couple different things as we go into the voting section aspect. I'll either go this direction or the other direction in asking. I will vote last.

The other thing is that it's not enough to give a yes or a no. You have to give why. You have to explain your vote. We do it electronically, but we'll ask you also to go around the room and explain it, as well. I'll explain last.

DR. HENNESSY: I'm wondering if I can ask a question of the sponsor at this point. Would that be allowed?

DR. BRANTLY: Of course.

DR. HENNESSY: Thank you. So I'm not sure who for the sponsor would like to address this, but I wanted to see whether the sponsor agrees that the protocol or the analysis plan for UPLIFT specified that the secondary endpoints would

not be analyzed or would be analyzed and only considered to be exploratory information if the primary endpoint, which was rate of decline of pre and post-bronchodilator FEV1, was not achieved.

DR. KESTEN: I've come up all the way here, but I actually would like to have our statistician specifically respond to your request about the approach in the statistical analysis.

DR. MENJOGE: My name is Shailendra Menjoge. I am a statistician at Boehringer Ingelheim. UPLIFT was a very difficult trial. The primary endpoints were unusual and particularly difficult. So we had to somehow make sure that we had enough alpha for the primary endpoints.

So we did put all of our alpha in for the primary endpoints. A P value of a little bit above 0.001 was kept for number of exacerbations leading to hospitalizations. That also came up during the EMC development and the charter.

So our interest was in actually looking for exacerbations and key secondary endpoints were time to first exacerbation and hospitalization. So

it is unfortunate that we had put all of our alpha into the primary endpoints.

That said, according to the prespecified analysis, really speaking of Dr. Buenconsejo is correct that we had to look at the secondary endpoints mostly as descriptive or exploratory and the P value should be considered nominal.

That said, I just wanted to also emphasize here that the evidence that we have in the exacerbation endpoint is very, very large. The log hazard ratio is five standards away from zero. So usually you expect about two standards away from zero to have a significant effect. So the evidence, we believe, is more than two independent trials we have given.

DR. HENNESSY: So just to clarify, you're asking for a label indication based on an analysis that you specified in the protocol would be interpreted only as exploratory.

DR. MENJOGE: I just want to further talk about that. If you strictly look at only one trial and if the endpoint was considered as one of, say,

15-20 endpoints, I would say that it would be a spurious finding. But I really don't believe, as a statistician, that one can argue that it's a spurious finding. There is a lot of evidence that we had before and everything should be considered as a part of the total evidence.

DR. HENNESSY: So that's a yes?

DR. KESTEN: Rather than going up there, I'll just try this one this time.

So just to clarify, though, we do have the VA study, which is the primary outcome had exacerbations that confirmed the results that we saw in registration trials.

Your points about the statistics, that we did not achieve the primary endpoint, are recognized and acknowledged in the data subsequently. It was tested. It is considered descriptive. However, we're asking you to consider that there is a very large database here on a clinically important endpoint that we did look at carefully in the UPLIFT trial.

We see tremendous consistency in that

database. It also confirms what we see in the VA study, registration trials, we see it in many subgroups. Also, it's what we expect.

So I think that's one of the main questions is the compelling evidence that exists and asking is there a drug effect here, and we believe that there is substantial evidence saying, yes, there is a drug effect here.

DR. BRANTLY: Dr. Schoenfeld?

DR. SCHOENFELD: I'd like to discuss the multiple comparison problem for a minute, because you asked the question earlier and it's come up again. This is one of the biggest paradoxes in biostatistics.

The way I usually explain it to clinical investigators that come to my office is I say does it make sense -- you've come in today and I have two appointments today with clinical investigators. I'm going to do two analyses today with two different clinical investigators.

Does it make sense that now, today, my P value for significance is 0.025 and not 0.05? If

you want to have a 0.05 P value, you better come back tomorrow when I don't have any appointments and you'll be the only appointment.

Now, everybody would probably agree that that makes no sense at all. But, in fact, the evidence from a finding is independent of what your plan was in the beginning. The evidence from the finding is based on the data of the finding. It has nothing to do with your evidence.

So then the question is why have all this rigmarole about primary endpoints and secondary endpoints and so on, which is what we're talking about. And, again, this has nothing to do with the evidence from findings. This has to do with decision-making.

If you have a single decision to make and then large numbers of different things that you're going to make the decision about, then you do have a concern, because if the null hypothesis is true, if there's no effect at all, there is sort of an increased chance that you'll make the wrong decision.

So I think that these primary endpoint things have -- definitely, these methods of avoiding multiple comparisons, which were used, for instance, in the statistical analysis plan of the UPLIFT study, do have a role, especially for a new drug that's unapproved and is going to be approved for the first time, and you want to make sure that you don't approve it on the basis of a spurious finding.

But I don't think they have a role in describing the effect of the drug, which is really, in a sense, what we're about. What we're about today is whether or not this can be added to the advertisement for the drug; that is, should it be included in the description of the drug.

In that case, I think it stands alone, except in the situation which Charlie Hennekens talked about. If you had three different ways of describing the same thing, you might also be in the position of looking at something three times to make one decision. In that case, I think multiple comparisons always has a role.

While I have the floor, something more germane to the mortality endpoint is another sort of theoretical concern, which is kind of, I think, interesting. That is, we know that we have this notion of level of evidence and we know, for instance, that if we have a large-scale clinical trial, it provides a greater level of evidence than a bunch of epidemiologic studies -- a bunch of observational studies. And that's well determined and that's sort of -- we didn't have any trouble with that.

Where we're having trouble here, to a certain extent, is how to deal with meta analysis, which is kind of a new problem. That is, what do we do when we're comparing a well designed, large clinical trial with meta analyses from other trials, and it's kind of a new problem. Philosophically, I think I would tend to favor the large-scale trial, especially if it's well designed for the endpoint that we're concerned about. Thank you.

DR. BRANTLY: Other questions,

particularly centered around mortality data? Dr. Hendeles?

DR. HENDELES: I have a question for Dr. Michele.

Does either Advair or Symbicort have, in the labeling, approval for reducing exacerbations?

DR. MICHELE: There is an exacerbation claim and indication for Advair.

DR. BRANTLY: Let me see if I can stimulate a little discussion about the mortality again. It's an important issue here.

So we have data that suggests that at least in the UPLIFT trial, that there may be a mortality benefit associated with this particular study. That's an important indication and, obviously, it's the world's best outcome variable in a lot of ways for a drug. So we have a little of a conflict on shorter trials that suggest actually that there is not a mortality benefit; indeed, there may be an increase in mortality with some short-term trials using a similar, but not an identical formulation.

The question is what is this telling us?

Dr. Hendeles?

DR. HENDELES: I'd like to first address this Respimat data. It doesn't make sense to me that the 5 microgram Respimat and the 18 microgram HandiHaler give the same area on the curves, saying that they have the same exposure, yet the Respimat has a greater systemic adverse effect.

If you look at cardiovascular, for example, how can it cause a cardiovascular adverse event unless the drug gets to the heart? So that part doesn't make sense to me.

The fact that there's a trend toward a dose response makes me wonder if either there is something in the two studies, like, for example, in the UPLIFT study, maybe people didn't inhale as deeply as the subjects did in the pharmacokinetic study. So maybe as much wasn't delivered or maybe the Respimat is a much more efficient delivery system than the dry powder inhaler.

But it just doesn't compute to me that you could have the same exposure, systemic

exposure, and have an adverse cardiovascular event with one formulation and not the other.

DR. BRANTLY: Dr. Schoenfeld, let me just ask a question to you as part of the discussion.

Is there a weakness in looking at mortality in short-term studies?

DR. SCHOENFELD: That's a good question. I think that the problem is that you're actually looking at a somewhat different thing. The mortality in short-term studies is going to be the short-term mortality, and it may be different in the long-term mortality over four years.

It's also true that I guess in the long-term study, there was a -- since it was designed -- it was more -- it was designed to look at mortality. They did do long-term follow-up, which they apparently didn't do in some of these other studies.

The problem with long-term follow-up has already been alluded to in some of the presentations; that is, if you don't do long-term follow-up, that is, ask everybody after four years

whether or not -- find out for everybody after four years whether or not they're surviving, then you have this problem that people sometimes drop out of trials and it's well known. I've seen it in a lot of data, my data. People drop out of trials when they get very sick and then they die subsequently, and their death is not counted in the dropout of the group and this can happen differentially. So this was mentioned.

So I certainly think that the best trial for looking at the adverse events is the UPLIFT trial, because it was designed for that purpose. It was designed as a trial to sort of have -- at least it appears, from what we've been told, at least, that it was designed as a large-scale trial for determining the full spectrum of the effects of this medication rather than a trial specifically designed for a specific purpose of showing efficacy in a different endpoint. So it seems like the best trial for making judgments.

My view of the mortality issue is I think there's evidence that there is an improvement in

mortality and that's largely from the UPLIFT study. It's conceivable that the -- and, also, an improvement in cardiovascular events. It seems to me that the Respimat data could just be a matter of bad luck in Europe, bad luck, in a sense. I don't know that there is a significant interaction between these results. In other words, the results are close enough to 1 that it could be chance that things didn't work well in Europe. It's a fairly small trial and it sort of remains unexplained.

Now, I noticed that they withdrew the claim for mortality in a previous meeting with a different drug for the same indication. The P value for mortality was, I think, 0.05 and we neglected to approve the mortality indication, although I actually voted to approve it.

Here, we're at a 0.03. There's really not that much difference between 0.03 and 0.05. I guess the reason that they withdrew it is because there is some data, extra data, outside the trial that would indicate that it wasn't the case and it would make maybe the 0.03 more suspicious.

You might want to comment on why you withdrew the mortality claim.

DR. KESTEN: Thank you for raising that issue, and I would like to take the opportunity to clarify. We interpret the data from the UPLIFT trial as indicating a mortality benefit or survival benefit. There is no other tiotropium HandiHaler data that has influenced the decision or additional HandiHaler data that would take us away from that.

Indeed, with the pooled analysis of the 26 trials of 17,000 patients, again, 12,000 patient years of exposure, we see that finding. Now, we recognize, though, here, the complexity that happens when we have the smaller numbers from the Respimat and having that kind of discussion.

So our decision here was we wanted to focus on the exacerbation efficacy endpoint in the discussions in the committee and, also, address those outstanding issues from observational studies and the early communication and focus on that. But, again, let me reiterate there is no additional HandiHaler data and we interpret it as you have.

DR. BRANTLY: Dr. Wolfe and then Dr. Platts-Mills.

DR. WOLFE: A small part of my question was answered by the last question and the response. The reason we have not been asked to vote on these discussion questions 1 and 2 is because the request for getting approval for mortality has been withdrawn.

So I think the two are very, very linked. You've heard just the company say that they had some concerns about the Respimat, which may or may not have been part of their decision to withdraw the request for an indication for mortality.

But I think it's reasonable to discuss these together. And I think that with the exception of the meta analysis, which I think there was a very good analysis of it by the FDA and, as was pointed out in your materials, a correction by the authors of at least part of the data, the rest of it is, at worst, neutral. In other words, it doesn't show -- the company says it prevents lies, but they are not even asking us to vote on that, so

that's not the issue.

So you've got the UPLIFT, which at least, to me, seems not to show significant huge decreases in mortality, but certainly doesn't -- there is nothing about it or the other studies on this product that show an increase in mortality, again, with the exception of the at least criticized meta analysis in the JAMA.

On the other hand, you have the smaller, shorter, smaller numbers, shorter duration, six months as opposed to four years, in this Respimat and, as I mentioned earlier, it is a larger dose and there at least is some suggestion of an increased mortality.

Again, we're not voting on that, because this product -- I don't think it's been submitted yet for approval from the FDA. I mean, you're not allowed to say that if it has been. Our discussion is simply saying same chemical, slightly higher dose, how do we interpret that, and I would argue we need to interpret the two together. The discussion of the two points, since there are no

votes at all, can, I think, easily and properly go together. What you come away with, for me, particularly because the company has already withdrawn the request, no comment or nothing will be made to change the label from what it is now on the HandiHaler and sort of reserve judgment on what happens with the other one, but informed somewhat about some risk information there.

DR. BRANTLY: Dr. Platts-Mills?

DR. PLATTS-MILLS: Can you answer a question? Did being in the UPLIFT study improve mortality? That is, I'm not talking about the comparison between the drug and placebo, but overall, it's a big enough study that you can relate it to population-based figures for COPD mortality.

So can you compare it to the -- that is, being followed this closely and monitored, does that improve mortality?

In relation to the Respimat data, one of the most striking things in the Respimat data was one arm of the study where the placebo group had no

mortality, which is always an extraordinary finding in a COPD study.

Could that be related to population-based? Then I have a comment.

DR. KESTEN: So I'll try and address each of the questions here. The first issue is, well, how does this compare to our population compared to the population as a whole, I suppose, is what you're referring to. We think we have a fairly representative population of patients who would be seen in the community. We did allow all sorts of medications, as Dr. Michele alluded to. Our criteria for inclusion were quite liberal. We had lots of patients with cardiovascular disease, musculoskeletal disease, gastrointestinal, psychiatric disease, as often you see in this population.

So we interpret the data from UPLIFT as being representative. We interpret the findings in a controlled clinical trial, so that caveat there. There is indication that there was lower rate or a lower hazard ratio for mortality with the group

treated with tiotropium.

Now, I just want to get to the other issue about Respimat which is in there and Dr. Wolfe also alluded to.

DR. PLATTS-MILLS: But I think you're missing the point.

Can you relate it to known rate of mortality in patients with COPD of this severity who are not included in a clinical trial?

DR. KESTEN: I'm not sure I can answer that question, because the disease itself -- in population studies, and included some of the population studies which we included in the briefing document, shows, compared to a matched population, there is a significant increase in risk for mortality by having COPD and, indeed, for having cardiovascular events by the nature of having COPD. I'm not sure if I'm answering your question.

DR. PLATTS-MILLS: No, no. But I think Dr. Tashkin definitely has figures for what the expected mortality rate over four years is of a

group of patients who are X percent Gold, 2-Gold, 3-Gold, 4-Gold.

DR. KESTEN: Now, I understand. Right. So there is population data. I'm sorry. Now, I understand.

Dr. Tashkin, do you want to address the specific issue of mortality rate in COPD and the relationship to FEV1?

DR. TASHKIN: Actually, in my presentation, I misspoke. I wasn't really quoting David Mannino's work, but rather Soriano's using a U.K. administrative database. In that study, the results were not broken down by severity, but the overall mortality from COPD, three-year mortality was 33 percent. I don't know what it was in UPLIFT in the placebo group.

DR. KESTEN: I would like to address the other point that you made and Dr. Wolfe was referring to in terms of the dose issue of Respimat 5 micrograms versus 18, because it has come up a couple times.

Mr. Chairman, may I just clarify that?

DR. BRANTLY: Yes.

DR. KESTEN: Also, Dr. Disse, with his expertise in pharmacology, perhaps could clarify that.

DR. DISSE: Can I have the slide from the adverse event dosing consideration, Respimat for fatal adverse events?

So here is, again, the studies which we used to address the dosing issues. They were one-year studies, with a reasonable number of patients, as indicated there, and compared 5, 10 and placebo.

Maybe we'll focus only on the numbers and ignore the incidence rates. All cause, with vital status follow-up, an appropriate measure for a mortality assessment, 9 placebo, 14 versus 17. That looks like an apparent increase.

But similar to the slide that also Dr. Michele has outlined, if you then look at the system organ class distribution, you find in cardiac disorders 161. You find in general death, sudden death, 306. If you add the two up, which you might do, it's 467.

Then respiratory system is against everything which we have seen in other tiotropium databases. So a high mortality by, I believe, chance in the Respimat 5 group. Gastrointestinal, 202. Neoplasms, 101. Respiratory neoplasms, 012. Nervous system, 201. Then some scattered cases in individual classes.

So I think that doesn't make sense. That doesn't give a pattern.

We further analyzed adverse events and serious adverse events for any dose relationship and, yes, you find it, but for those adverse events which are anticholinergic mechanism-related. So it starts with dry mouth. It's dyspepsia. It is urinary retention, urinary tract infection.

There you find the signal in a dose-dependent fashion. If you then use this sensitive signal and compare the database for Respimat versus the database for HandiHaler, the adverse event signal is similar. So from that point of view, we have concluded, no, we don't find evidence supporting a dose response relationship for

mortality, but certainly we find it for typical anticholinergic events.

DR. BRANTLY: Dr. Platts-Mills?

DR. PLATTS-MILLS: I just wanted to make a final comment. I was impressed with Dr. Pinheiro's analysis of the meta analysis and I have had great trouble with meta analysis in the past. I'm increasingly impressed that the criteria for choosing studies that go into meta analysis controls the analysis and it can be done in a thousand ways with a thousand different intents.

DR. BRANTLY: So I just wanted to go back and, one more time, frame Dr. Platts-Mills' discussion and see if I can also get at that just a bit. What you were speaking about is there is a center effect.

That is, we know that oftentimes these clinical trials are conducted in really centers of excellence regarding therapies and that oftentimes just by the fact of being at a center, patients have decreased mortality and some improvement in outcomes.

It would seem like that issue would be taken care of by the fact that it's randomized, placebo-controlled, though.

Dr. Hendeles?

DR. HENDELES: I have a question for Dr. Tashkin. In the TORCH study, as I recall, there was no difference in mortality between the salmeterol-fluticasone. Maybe you could refresh our memory and how that may differ from the UPLIFT study.

DR. TASHKIN: I'd like to respond to your question, but we have an expert here who has published on the results and the TORCH data with respect to the impact of salmeterol on mortality results, and perhaps Dr. Suissa would like to comment.

DR. SUISSA: My name is Samy Suissa. I'm from McGill University-Montreal. I do have conflicts. I was paid an honorarium to attend this meeting by Boehringer Ingelheim and I do receive research grant funding. I have been a speaker and attended at board meetings for Boehringer

Ingelheim.

Regarding the TORCH study, which is another very large-scale, randomized control trial, a two-by-two factorial design, where the LABAC, long-acting beta-agonist component, and the inhaled corticosteroid component were evaluated.

Indeed, I believe maybe this committee has looked at that study already in the past, where they found that a combination therapy compared to placebo almost reached statistical significance in reducing mortality.

I believe Dr. Tashkin wants me to speak about my further analysis of these data, which have shown, by a two-by-two factorial analysis, that, in fact, what was driving this reduction in mortality was the long-acting beta-agonist component of salmeterol rather than the inhaled corticosteroid component. And this, again, goes along with the discussion that we've had here regarding the effect on bronchodilation in COPD as opposed to asthma and the beneficial effects of bronchodilation regarding mortality.

So, in fact, we can even say that from that perspective, there is very good concordance between the TORCH results regarding bronchodilator effects on mortality and this UPLIFT study that we are seeing here, also, regarding bronchodilator effects on mortality.

Does this answer your question, Dr. Hendeles?

DR. HENDELES: Yes.

DR. BRANTLY: Any further comments on the two questions associated with mortality? Mr. Terry? I'm sorry.

MS. HOLKA: Andrea Holka. That's okay. My question relates to the Respimat trial, the 372. I'm just wondering if there are any plans that the sponsor has to extend this trial out to more years or whether or not you plan to take on another trial to watch this mortality.

DR. KESTEN: Yes. I think that's also an important issue. With the Respimat program, as has been described, we are looking at smaller numbers. We're looking at a smaller dataset when we look at

the totality of our experience with the extensive HandiHaler clinical trial program. So the important issue is to generate information and we do plan to conduct a larger long-term trial comparing the relative benefits and safety of tiotropium Respimat to that of HandiHaler.

DR. BRANTLY: Dr. Newman?

DR. NEWMAN: If I could just follow-up on that?

Are there any plans in that -- and I think it's important and a great idea to be doing that study. Are there plans in that or what are the plans for how you'll look at the mortality signal in that?

Will it be like what was done in UPLIFT or are there some other approaches that you're likely to take to examine mortality specifically? I'm glad to hear that that's going to be happening.

DR. KESTEN: We think it is important and that's the reason for doing it. We believe that the standard that we've set and established in our experience with UPLIFT gives us guidance here. So

we will be collecting vital status information of prematurely discontinued patients.

We are planning on establishing an independent mortality adjudication committee. We're going to have a data safety monitoring board. We're into just the planning stages and we're looking forward to discussions and suggestions on this trial.

DR. BRANTLY: Dr. Honsinger?

DR. HONSINGER: Just a comment. I'm glad that the sponsor withdrew the application for us to review the mortality data and to make a decision regarding the Spiriva HandiHaler.

Certainly, the data looks like the Spiriva HandiHaler doesn't cause mortality. It may actually improve mortality. But when we have to evaluate then on the basis of the limited data and the limited study on Respimat, it would have been hard to make a decision that we should approve that as a package insert.

DR. BRANTLY: I'd like to make a stab at providing sort of a summary of the committee's

feelings regarding the mortality data and where we should go with that. I'd like the other committee members to add into that.

So I would say, number one, that the UPLIFT data is very compelling, very important; that the conflict with the shorter-term data regarding the Respimat is a bit concerning, but is likely not to bear fruit when this is taken out on a longer period of time; and, that our encouragement would be that this would be pursued as an indication in the future of this very important outcome variable.

Anybody to add to that?

DR. NEWMAN: Well, I'm not sure I would go quite as far as you did with that, Mark, but I would agree that the UPLIFT data is -- I think this was already said -- suggests that at least we're not seeing an increase in mortality. In my opinion, I think it trumps the meta analysis for the reasons that have been discussed.

I don't know what to make about the Respimat data, except not to have it at this point

override the data from UPLIFT. I guess that's about as far as I would go with it and just add that I'm pleased that there is going to be a larger study done.

DR. BRANTLY: Dr. Chowdhury?

DR. CHOWDHURY: Thank you for your summary comment. It was very, very helpful for us to hear that. I just wanted to probe a bit more about your comment, the company's comment regarding the possible procedure for the indication for mortality.

We also hear -- acknowledging that Respimat has this finding which sort of goes in the direction opposite to the HandiHaler. The explanation for that is really not there, acknowledging what Dr. Hendeles has said, possibly related to exposures, related to the two products.

My point here that I wanted to discuss a bit more and perhaps comment on is before pursuing the mortality potential as an indication, what further studies would the company think would be necessary, if any?

DR. BRANTLY: Comments?

DR. HENNESSY: Given we have a large randomized trial that doesn't suggest an increased risk of mortality and does suggest a reduced risk of mortality and that any randomized trial -- that a randomized trial, particularly if this outcome, is going to be much more convincing than any non-randomized study, I don't know that we need any additional data concerning the concern about elevated mortality rates.

DR. LESAR: Tim Lesar. My only comment about the mortality is I kind of look at things a little bit differently. There are a lot of other variables. While patients may have looked similar at the start in randomization, at four years, do the populations again look the same in terms of what other medications they're on?

Are there intercurrent illnesses that serve to recur? How much beta-agonist are they using? So there are some things that didn't occur at the analysis at that point, but did occur at the beginning.

So over long periods of time, patients become different, and does that occur similarly within the two populations? That's my only comment about comparing mortality.

DR. BRANTLY: Dr. Knoell?

DR. KNOELL: Thank you. I don't have much to add. Maybe it's my pharmacy background, but I keep going back to the picture of the absorption values, systemic blood levels after inhalation.

One thing that did strike me is that at the early time points, to reach peak plasma concentrations, there's an amazing amount of variability between those three different delivery platforms.

In the case of the 10 microgram dose of Respimat, the peak levels at the highest point are extremely high relative to the other two groups. So that does continue to raise concern for me.

Related to that, we've talked about the convincing evidence that you could not relate blood plasma levels of the drug to well established side

effects as a function of anticholinergic activity. I believe that.

Something we haven't talked about today, and I would assume that you're interested in pursuing, but cannot yet do given limitations in the field, and that is the receptor responsivity of the patients and the possibility that different patients respond differently to similar doses of the drug because of changes in the way their receptor interacts with the lung, although we can't do that yet, I understand. In the future, that may be possible and that may be a way to get at better understanding of potential toxicity.

DR. BRANTLY: Dr. Wolfe, you had a comment?

DR. WOLFE: Yes. I think someone, I can't remember who, from the company, when someone in our group asked about number needed to treat. The figure that was given out was you need to treat 100 patients to prevent one death.

I think Dr. Platts-Mills' question is a good one. In this randomized control trial,

admirably long, admirably large, the UPLIFT trial, we see this difference, although it's only going as far as the non-hospitalized version of exacerbations. But do we really think -- I'm pursuing the same question that was raised by someone else. You raised the issue about the company possibly pursuing a mortality benefit.

Are there other drugs right now that have been approved with a mortality benefit for COPD? I don't know that.

FDA?

DR. MICHELE: If I could respond to that. There are no drugs that have a specific indication for the improvement of mortality for COPD. In the Advair label, the TORCH study is described with the results of the mortality data in the label.

DR. WOLFE: So this would be the first drug, if someone sought that, and one might want to look at the mortality data from some of these other drugs sand see how it compares.

There was no reason for that to be presented today, but we also weren't discussing

whether it should be approved for a mortality indication. So I think that before ever getting to the point of thinking about that, it would be worth the FDA and anyone else who is interested looking at the data, of which there is quite a bit, on some of these other treatments for COPD.

DR. BRANTLY: Dr. Platts-Mills?

DR. PLATTS-MILLS: I would encourage not to pursue mortality data, because this is a disease of which everyone dies fairly rapidly and the longer you go on with the study, the more inevitable death will become. To go beyond four years would be an extraordinary achievement.

I would encourage focusing on quality of life and, obviously, an interaction with pulmonary rehab or the interaction with other aspects of management to try and control exacerbations would be very interesting.

That is, what do you provide patients with so that they can handle their own exacerbations at home? I think that's a much more productive line than focusing on the mortality.

You're dealing with adult men who are already down to 30 percent of their lung function and pursuing survival is not a very good idea.

DR. BRANTLY: Dr. Schoenfeld?

DR. SCHOENFELD: I think this issue of whether the number needed to treat is the relevant statistic here, is an interesting one to me, because yesterday, of course, that was, I think, an important issue was the number needed to treat.

I think, again, this is different on a secondary claim. This is a different issue on a secondary claim versus a primary claim. That is, it seems to me that if your primary claim was mortality, if, in fact, this drug had no symptomatic effect, then I think the number needed to treat is a relevant quantity. And you might ask the question, if the drug had nothing to do with anything but mortality, is the kind of difference that you're seeing in this population worthwhile, and that would be a question.

But I think that the issue is not that. The issue is, rather, the primary indication is, in

fact, symptomatic, the forced vital capacity in dyspnea, as measured by FEV. The question is what are the secondary effects of this treatment. Then I think it's, again, descriptive; can you add mortality to that advertisement?

So the question then is not a number needed to treat question, but just what does the data show.

DR. BRANTLY: Dr. Chowdhury?

DR. CHOWDHURY: If I can just go back and comment on Dr. Wolfe's question about mortality indications throughout the COPD trials. The answer is no. Advair was the drug that we discussed at this committee a couple of years or months ago with that question and the P value was not significant, missed it marginally. And the committee was of the opinion, and we ultimately went in the direction, of not giving a mortality claim. A mortality claim for any drug, particularly a drug for COPD, would be a substantial claim. It is a substantial claim.

So I just wanted to make sure that we get feedback from the committee. But for this

particular drug, based on the existing data, should the committee recommend or would the committee think that more studies or more data needs to be generated before one would consider a mortality claim?

DR. BRANTLY: Dr. Honsinger?

DR. HONSINGER: In answer to your question, I think we have adequate data for this Spiriva HandiHaler. But there's the onus of this other study and another formulation of tiotropium. And I think we need to remove the onus of the fear of other tiotropium before we say that it doesn't change mortality data.

So I think we can say that it doesn't cause increased death. Before we say it saves lives and prevents death, we need to know more about tiotropium in other studies and other formulations.

DR. BRANTLY: Dr. Schoenfeld, did you have another comment?

DR. SCHOENFELD: Well, I guess the implication of what you said was that a mortality

claim is treated differently than other secondary claims, that it becomes sort of a primary claim.

I guess then that requires two well controlled studies. So what would be suggested by that, if you're going to treat it as that, what obviously is needed is another study that shows a mortality benefit.

DR. BRANTLY: Dr. Chowdhury?

DR. SCHOENFELD: That would clearly do it.

DR. CHOWDHURY: I just wanted to come back. It's not necessarily that all the claims in this application -- and mortality is a claim, and I think one can be open to whether one study would do it or not.

If you really have a drug that has a mortality benefit, doing a subsequent study for the same drug with the same question becomes something of a difficult issue. Here, the question is, going back to what Dr. Honsinger just mentioned, we have two products with the same active moiety seemingly not agreeing with each other.

In that situation, if one is to pursue a mortality claim for one product, what do you think one should do? I mean, one thing that we heard is remove the mortality sort of question from that product that Dr. Honsinger mentioned, as I think we first hear. I just wanted to hear if anybody else has anymore comments on that.

DR. PLATTS-MILLS: Can I just comment very briefly on Dr. Schoenfeld's comment?

Doing a four-year, 5,000-patient study again is an incredible thing to ask. This is an extraordinary database that we've got and the results are very clearly what they are. They're there. I think asking for another one is extraordinary.

DR. SCHOENFELD: There is also the issue as to whether mortality is a -- whether we can treat mortality in this setting in the same way that we treat mortality, for instance, in cancer or in other settings in the sense that this is a very, very highly symptomatic disease in which people are extremely disabled.

The lung volume reduction study, which was a major study in this disease, actually considered mortality as a secondary endpoint. Basically, they used -- at least in my memory of the study, it was sort of a non-equivalent -- it was an equivalence, a noninferiority endpoint.

They wanted to improve patient symptoms and they just wanted to be sure that mortality wasn't made worse by the treatment. So in a certain sense, mortality doesn't become the major -- - at least in that trial, in that interpretation, mortality was not the major issue. The major issue was quality of life, basically, and the problem with quality of life, of course, is it's very hard to measure. So in that study, they did a six-minute walk as a measure and in this study, I guess, it's lung function.

DR. BRANTLY: So I'd just like to go back to this discussion one more time. I think that in pulmonary medicine, we have not thought about COPD and the concept of it reducing mortality. I think that it's a new thought. It's something that we

never believed that we'd ever come to, quite frankly.

It remains an exciting outcome variable for me, and I would like to see this pursued with greater vigor at the present time. Whether that's going to end up having another, unfortunately, long-term study or whether there needs to be resolution on the other drug as far as its mortality, I really would encourage going for the gold regarding this in a lot of ways.

Dr. Hendeles?

DR. HENDELES: One thought I had is is it possible that the bioavailability or pharmacokinetic studies were done in healthy volunteers and not in patients with COPD.

DR. CHOWDHURY: Is that a question or just a comment?

DR. HENDELES: It's a question, because then I have a comment depending upon the answer.

DR. DISSE: It was, of course, done in both, but the data shown by us and Dr. Michele were inpatients.

DR. HENDELES: Thank you.

DR. BRANTLY: With those comments, I'd like to move on to our first voting question. Again, it's my interpretation, unless somebody disagrees, that questions 1 and 2 are really linked to each other and that we've provided the agency with the appropriate guidance.

DR. CHOWDHURY: Yes. They are linked to each other and you have. Thank you very much.

DR. BRANTLY: So question 3, do the data from the trials 205.235, the UPLIFT, and the VA study provide substantial and convincing evidence to support the claim that Spiriva HandiHaler reduces COPD exacerbations, and if not, what additional data is needed?

We'll go ahead and start the vote, please.

Does anybody want to clarify the question? Is everybody clear on the question? You want some discussion. Sorry to hurry this.

Dr. Hennessy?

DR. HENNESSY: So from the VA study, it

looks like there's a 4.4 percent absolute reduction in exacerbation over six months, which, over a year, if you do the math, it's 8.8 percent. In the UPLIFT study, it looks like the absolute difference is about 12 percent per person per year.

Those numbers are very consistent, although I want to be careful about considering results from exploratory analyses when looking at the label. I think we can consider the UPLIFT study to be supportive of the primary data from the VA study, particularly since reduction of exacerbations was the principal endpoint of the VA study.

DR. BRANTLY: Dr. Knoell?

DR. KNOELL: Thank you. Just a quick clarification. You mentioned early on in the day that you actually did look extensively at quality of life indices. We haven't talked about them, for the most part. I did pull up Dr. Tashkin's paper and clearly there is a nice figure in there showing, with the St. George questionnaire, that there were differences.

But could you comment further? The bottom line is did these patients feel better over the course of four years?

DR. KESTEN: Thank you for asking that question, because it's one of the critical issues. Are we making patients feel better here? We have done a number of studies with the St. George's Respiratory Questionnaire as a questionnaire measuring health-related quality of life specific to COPD patients.

Now, I recognize that there is debate about the questionnaire, but it's probably the most widely used questionnaire in COPD. We have seen consistent reductions in -- we have seen consistent improvements in the St. George's Respiratory Questionnaire in our registration studies. We also had conducted a primary outcome study on it in France and had that a positive result. In the UPLIFT study, we see the scores improving over four years with treatment.

So we believe that the data is very strongly supportive of exactly what you're

referring to, that there was symptomatic improvement that sustained.

DR. BRANTLY: Dr. Platts-Mills?

DR. PLATTS-MILLS: Can I pursue a question that I was asking this morning? In asthma, active smoking has a profound anti-inflammatory effect. That is, you can actually measure decreased exhaled nitric oxide, decreased eosinophils in the peripheral blood, decreased ECP in secretions. It would pass muster as an anti-inflammatory drug.

Therefore, if your drug is addressing the issue of mechanism of decreased exacerbations, if your drug was an anti-inflammatory effect, then you might expect, as we see in asthma, that anti-inflammatory drugs have very little effect in active smokers; that is, the inhaled steroids appear not to work in patients who are currently smoking.

So the question is, can you see any effect of that kind in COPD, because if you can't see any difference, it argues very strongly against

there being an anti-inflammatory or some other anti-something effect, i.e., that the only effect is bronchodilator?

DR. KESTEN: Maybe I should clarify my previous comments. The basic laboratory investigations on antimuscarinics are just that, in the lab only. No one has shown that there's clinical benefit of this putative anti-inflammatory lab stuff. And we do believe that the major benefit and the reason we're seeing the exacerbation reduction relates to the ability of keeping the airways, the pipes open and reducing lung volumes. It's an effect of sustained airway patency, providing that throughout 24 hours. And I think our data is consistent with that, and we are not proposing other mechanisms.

DR. BRANTLY: Dr. Michele?

DR. MICHELE: I just wanted to add a clarifying comment with regard to the St. George Respiratory Questionnaire. There was a statistically significant improvement in UPLIFT, but I did want to mention, as is noted in your

background package on pages 101 and 102, that while the results were highly statistically significant, they did not reach the clinically important difference of four, which is considered kind of the threshold for that.

DR. BRANTLY: Dr. Wolfe, you had another comment?

DR. WOLFE: In the briefing package and, to some extent, in the presentation by the statistician before, we have the situation where, in the VA study, the primary outcome was reduction in exacerbations and it seemed to have worked there, but the primary outcome in the UPLIFT study was reduction in the slope of the FEV1 before and after. And it didn't work at all, and, therefore, the secondary outcome can be just looked upon as exploratory.

So the question I'm raising is I believe that FDA has, as a standard for approving a drug or adding a new indication, that there need to be data from two randomized control trials, and we essentially have it from one. The other one is

looked at in an exploratory kind of way.

The phrase is used it's supportive and everything, but I just want to ask the FDA, is it not the case that you need to have data from two randomized trials, where presumably it was the primary outcome variable, to say, yes, we have two different sets of data that show that there is a reduction in exacerbation?

DR. CHOWDHURY: The substantial and convincing evidence is the standard that we use for a labeling claim. Generally, it has translated for most of the situations, requiring two studies. However, there are exceptions to that and there are situations where one study may be adequate for approval if the evidence is strong and the evidence is supported by other supporting information.

In fact, there is an FDA guidance document that we call the effective document that talks about situations where one study may be enough. This is a situation that we often deal with, and the situation here is kind of that, where we have one study where the primary endpoint is

exacerbation, as you mentioned, the other one which is not. And we do not necessarily always apply the two-study principal all the time for all the claims.

So having said that, I would like to take this opportunity to perhaps invite Dr. Permutt, who is our division director in the Office of Biostatistics, to comment on this secondary endpoint in the UPLIFT study. Thank you.

DR. PERMUTT: Tom Permutt, Division of Biometrics II. On the immediate question, as Dr. Chowdhury says, the standard is substantial evidence based on adequate and well controlled studies, which we've taken to mean the plural to be significant in most cases. But as he says, also, there are exceptions. One of the most important exceptions is the one that he raised earlier, that it's often not desirable ethically to repeat mortality studies when there are unclear findings.

Dr. Chowdhury has also asked me to comment on the question that came up earlier about the FDA's view of secondary endpoints. And that's

also somewhat complicated, as you heard from Dr. Buenconsejo and one of the sponsor's consultants.

We do exercise judgment to avoid suppressing important information simply because it wasn't foreseen in the planning of the study. On the other hand, one has to consider really the possibility of doing studies in drugs that don't have the desired effects and what happens when we apply various inferential procedures to those studies.

So in this case, if the UPLIFT study had produced a statistically significant result on the FEV1 measures and on nothing else, I don't think that the applicant would be here telling us how important exacerbations are. I mean, they are important, but we wouldn't be told that we couldn't approve a labeling supplement on the primary endpoint because it wasn't supported by the secondary endpoint.

So if you take seriously the notion of a Type I error of finding an effect when there is no effect, we clearly had the whole 0.05 probability

of making that error, of making that incorrect finding, and we clearly have added to that, if we choose to, the probability of making a finding on this other variable.

Now, there are reasons to think, as Dr. Lee wrote in the briefing document and some of you have commented, that given the very high nominal significance and the corroboration from the other study, that we're not adding very much to the probability, but we are adding something to the probability.

I'd also like to say something, because it's also relevant to this question, about what the regulatory situation is here. So we're not actually discussing providing or withholding a treatment from any population here.

What we're asking you to discuss is a rather technical point about -- or even, for that matter, of suppressing the information about the results of this study. You've heard them. They will be published. They will be discussed in a variety of forums.

What we're discussing is whether there can be an FDA-endorsed claim for these effects. I think my personal feeling is that that is a situation in which we can afford to maintain standards and we don't really need to stretch to try to find a way to make these important data available.

I've heard the word "indication" here several times and I'm puzzled by it, because neither the prevention of exacerbations nor the mortality claim is an indication, as I understand the word. It does not say in what patients it is indicated to treat with this product. It's merely, as Dr. Schoenfeld said, a kind of advertisement and a special kind, one with official endorsement to it. So that's the regulatory situation we're in.

DR. BRANTLY: I think Dr. Schoenfeld had his hand up fastest. So I guess this is sort of the interesting issue as to what is raised here, which I'm not sure what the answer is, what is the standard; what should the standard be for essentially not an issue of indication, but simply

an issue of what the sponsor can tell doctors and patients, if they choose to, in their advertising claim; that is, what can they basically say is known about this drug? That's the issue.

So the question then is, is there substantial evidence of this indication, despite the fact that it wasn't -- in the biggest study, the clearest study, it wasn't the primary indication. I personally think there is substantial evidence.

So it will be Dr. Newman, Dr. Wolfe and then Dr. Michele.

DR. NEWMAN: I guess I want to hear more from people here on this point, because I'm sitting here struggling with the concept that one designs a study with primary endpoints, with a data analysis plan for secondary endpoints that only get seriously considered -- we heard from the statisticians that this is the way we went into this.

What does it mean to then post hoc say, "Well, that doesn't matter. We're going to go

ahead and take the interesting secondary endpoints that we want to pursue and add those to the package?"

DR. BRANTLY: Dr. Wolfe?

DR. WOLFE: We've seen this data, but it's, I think, relevant to the discussion we're having. In the VA study, the exacerbation P value for any exacerbation was 0.037, which was significantly, obviously, and with hospitalization, it was 0.056.

In the UPLIFT study, where, as we've agreed, this was a secondary outcome, the primary one failed, the percentage of patients with an exacerbation, the P value was 0.35, and the patients with hospitalization due to exacerbation, the P value was 0.18.

Now, as Dr. Michele pointed out, when you went into some elaborations of that time to exacerbation and so forth and so on, there were some differences there, but that was not what the even secondary outcome was, as I remember. It was the percentage of patients who had an exacerbation.

So that aside from the issue of whether this is the primary or the secondary outcome, it was not statistically significant.

DR. BRANTLY: Dr. Michele first and then Dr. Schoenfeld.

DR. MICHELE: Dr. Schoenfeld, did you have a comment on what he just said? Because I have a different topic.

DR. SCHOENFELD: Well, I thought -- and maybe the people from the sponsor -- I thought that the measure of exacerbations that was primary in the UPLIFT study was, in fact, the time until the first exacerbation. That's correct, isn't it?

DR. KESTEN: May I clarify? Yes. So we specified two secondary endpoints in our statistical analysis plan and the data were analyzed based on having a completed, locked, blinded dataset. Those were time to first exacerbation and time to first hospitalization.

Just to also clarify, if we had done a 10-year trial with tiotropium, the proportion of patients with an exacerbation would probably be 80

to 100 percent. Eventually, everyone is going to have this event and that's why it was important in the long-term study to use time to first event.

DR. SCHOENFELD: But when you design a trial, there are two issues, actually. There is not only the issue of what is the important sort of physiologic, biologic or patient-centered effect that you're going to measure, but there is also the question of what is the best way to analyze that effect. And the design of the trial, its duration and the way it's designed determine how you're going to analyze that effect.

So in some trials, the occurrence of the effect would be the best way to do that. Sometimes, the number of such would be the best way. Sometimes, the time until the event would be the best way. So that decision is usually made before the trial is designed or before the trial is analyzed. So in a sense, their method of measuring it was time until, because it was a long-term trial, and that was statistically significant. So I don't think that that comment is an indication of

sort of that the result might be spurious, because it isn't an issue.

DR. BRANTLY: Dr. Wolfe?

DR. WOLFE: The question we're being asked is, does it provide substantial and convincing evidence to support the claim that Spiriva HandiHaler reduces COPD exacerbations. That's the question we're being put.

Whereas in the VA study, at least for the non-hospitalization ones, the answer was yes. In the hospitalization ones, it was no. That same question, again, what we're voting on, neither of those measures were statistically significant. That's the question we're voting on.

DR. BRANTLY: I think it reduces -- "reduces" is actually, interestingly, vague. I'm sure this question is purposely vague, because "reduces," I think, as this meaning, means that -- really, what we're actually being asked is, is there evidence that over the long course, it will reduce the number of exacerbations patients have, and that could occur.

Like you do in most of clinical medicine, you extrapolate beyond clinical trials. What we're trying to see is if a patient takes this treatment, whether that patient will have less exacerbations overall over their life span, and if you reduce the time between them, you reduce the exacerbations just as well is if you reduce the number in one year, which is the other endpoint.

DR. WOLFE: But what we're talking about is an advertising claim. Your point is absolutely right. The advertising is not going to say the time to the first, whatever; it's going to be does or does not reduce exacerbations.

DR. BRANTLY: Yes, which could mean either in this case. What I'm saying is that that's vague enough. It is an interesting question.

Would you reword the claim so that it covers both endpoints?

DR. WOLFE: Whoever said that we're not voting on it, it's not an indication. It's essentially a benefit claim, which, if it gets in

labeling, it can be used in the advertising and would have a distinct advantage. But, I mean, the way in which it's worded in our question is probably the way it might get worded in the advertising. I'm just simply pointing out that the UPLIFT doesn't confirm that at all.

Dr. Michele had something else.

DR. MICHELE: Yes. To further clarify all of this discussion here, Dr. Schoenfeld very astutely picked up on the vague wording here, which was intentionally worded as such, because we didn't want to detract from the issue of does it improve COPD exacerbations or not. How the claim is worded is a totally different issue.

I just wanted to provide a bit of clarity to Dr. Permutt's very nice discussion of the primary versus secondary endpoint and specifically to clarify the terminology for indication.

So while this would not be the primary indication for this drug that brought it onto the market, in other words, the first indication for approval, it would indeed be an indication. So a

bit of semantics, just to clarify.

DR. BRANTLY: Dr. Newman? No.

Dr. Platts-Mills?

DR. PLATTS-MILLS: Can I address the issue of the primary and secondary claims? The company, as far as I can see, has this really exciting idea that this continuous treatment for four years might actually decrease the decline, which would be, obviously, an extraordinarily important thing, if they manage to show it, and actually proving that there is no effect is almost equally important.

It's a major biological contribution to understanding COPD. That's really important to me. Therefore, their decision to make that the primary thing was made ages ago. I don't know when it was made. What, in 1995 or something? Somewhere back in the dark ages.

To say somehow that we're not allowed to look and not allowed to take seriously results that come out of it is very anti/against what really happens in clinical trials. That is, in clinical

trials, the idea that in 1995, you're going to know what the real outcome in 2009 is is ridiculous and I think it would be a major disservice if this committee implied that analyzing the data and presenting the data, we were not allowed to look at it because someone 10 years earlier had said, "Oh, I think something else is more important."

DR. BRANTLY: Dr. Terry?

DR. TERRY: In the studied drug group in the UPLIFT study, the time to first exacerbation was significantly longer. What I wanted to know is, did that effect persist? There were a number of individuals in both the experimental and the control group who had a second and third and a fourth exacerbation.

Was the time interval between the first and the second exacerbation and the second and the third greater in the Spiriva group than in the control group?

DR. BRANTLY: Would you like to comment?

DR. KESTEN: So there are a couple issues here which relate to that, because that gets to a

very complex issue when, after you've had a first event, there are interventions that can influence these subsequent risk. However, that being said, we have looked at that. I'll ask our statistician, Dr. Menjoge, to address that first and then another point.

DR. MENJOGE: We looked at the number of exacerbations in many ways. We looked at the time to first exacerbation, as well as time to second and third and subsequent exacerbations. You can imagine, in four years, there were plenty of exacerbations some of the patients had.

So in all of those, the results were very consistent. Our hazard ratios remained somewhere around 0.85, sometimes a little less, sometimes a little bit more. But overall, they're just really insignificant.

Have I answered your question?

DR. TERRY: So that means the time interval between the first and the second and the second and the third in the Spiriva group was a significantly longer interval than between --

DR. MENJOGE: Correct. That's exactly correct.

DR. TERRY: Thank you.

DR. KESTEN: Just one more point to Dr. Platts-Mills, and I thank you for the comment there. That's certainly our views.

I wonder if I could ask Dr. Suissa to also comment from his point about exacerbations and the primary endpoint and the issue looking at the other endpoints.

DR. SUISSA: Samy Suissa. The one thing that I think we have to notice here -- well, two things. I think that the protocol -- I agree with you. The protocol was written a long time ago and it probably is absurd to many people to see that you basically don't look at any data if you don't pass the first P value, and that is something that I have to say is absurd.

I think it's important also to note that the authors of the study used the state-of-the-art methodology to analyze this decline in lung function. What we see here is a state-of-the-art

method, mixed models, random effect, to analyze these data.

In fact, the FDA statisticians actually confirmed that analysis, until two years ago, when I published a paper that reminded the scientific world about a bias that was discovered 100 years ago by Sir Francis Galton, who talked about regression to the mean phenomenon.

In fact, what we have here in terms of these slopes of FEV1 decline, we have a major effect of regression to the mean. It's maybe not noticeable to you, but about 20 percent of the patients are not contributing any data to this decline in lung function. So out of 3,000 patients in each arm, it's about 2,300 or 2,400 that are actually contributing data to this decline. The ones who were excluded are probably the most severe ones, and these severe ones, because of regression to the mean, would have a different slope of FEV1.

So if you ask my opinion, my opinion is that I do not believe these two slopes. I do not believe that the two slopes are equal and I cannot

say whether the two slopes are actually different, whether the decline is different. And in view of this, I would not put any value to any of the data on FEV1 decline because of our friend, Sir Francis Galton, 100 years ago, talking about regression to the mean. However, if we talk about exacerbation data, then time to first exacerbation is much less affected by such dropouts, because all patients are included in that analysis.

DR. BRANTLY: Have we had sufficient discussion to vote on this particular question? If so, let me go back and just go over the electronic voting system for a moment.

Each of you have three voting buttons on your microphone, yes, no and abstain. Once we begin the vote, please press the button that corresponds to your vote. After everyone has completed their vote, the vote will be locked in and then the vote will be displayed on the screen. I will read the vote from the screen into the record and next we'll go around to each individual and state their name and describe why they voted

the way they did.

So let me go ahead and reread the question one more time. Do the data from Trials UPLIFT and VA study provide substantial and convincing evidence to support the claim that Spiriva HandiHaler reduces COPD exacerbations? Yes, no or abstain, you can vote now.

[Voting.]

DR. BRANTLY: Everyone press their vote one more time, please.

DR. HENNESSY: My attend button is blinking and my yes and no buttons are not blinking.

DR. BRANTLY: Do we want to try the vote one more time? Everything is fine. Great.

Can we have the display of the information? The voting results are yes-11, no-1, abstain-zero.

I'd like to begin over here with Dr. Knoell in justifying his particular vote.

DR. KNOELL: Thank you. I voted yes. I thought both trials, in my opinion, shows

unequivocal evidence of benefit. I note that the pulmonary function rate of decline had not decreased, but had improved and was sustained. Patients generally felt better, didn't reach statistical significance, but there was a strong trend, and exacerbation rate was improved.

DR. PLATTS-MILLS: I voted yes for basically the same reasons. I thought both studies showed a clear and convincing effect and, in addition, that that was biologically plausible given the bronchodilator effect that was obvious from the drug.

DR. SCHOENFELD: I voted yes for similar reasons.

DR. WOLFE: I voted no for, I think, reasons I implied, which is, as worded, the question says does it support the claim that it reduces exacerbations. The severe exacerbations were not reduced in the VA study, and from a statistical standpoint, neither type of exacerbations were reduced in the UPLIFT study.

DR. BRANTLY: I voted yes, because I

believe the combination of both studies support the effect of reduction of exacerbations.

DR. NEWMAN: I voted yes, with some hesitation, in part, because I don't care how stupid we want to say we used to be when we designed studies. I think that when we change the rules after we've got the data, it calls into all kinds of questions for me whether we're doing the right thing and causing the question, the whole concept of having primary and secondary endpoints.

So that was the one point of concern that I had. But at the end of the day, I don't think that a vote either way here is going to deprive people of a medicine that is going to benefit them.

DR. LESAR: Timothy Lesar. I voted yes for the reasons already stated and, also, with some of the same reservations.

DR. TERRY: Peter Terry. I voted yes for the reasons already enumerated.

MS. HOLKA: Andrea Holka. I voted yes, and just a comment. I don't understand trial design. I don't understand -- well, I understand

primary and secondary endpoints, but I don't know all the history and how this all comes about, how this all works together. It's very interesting for me.

But as a patient representative, what I can't ignore is the data, regardless of primary or secondary endpoint. I think if we had seen secondary endpoints that had fallen off the deep end, I don't think that we would go back and forth and question those. They would be quite obvious and we would look at those. So I did vote yes.

DR. HENNESSY: Sean Hennessy. I voted yes based primarily on the results of the VA study for which reduction in exacerbations was the primary endpoint and then the UPLIFT study providing supporting information.

If I was making my vote just based on the UPLIFT study, I would have voted no. Not that I don't believe the result. In fact, as a journal editor, I would accept a paper that said that it was effective, but I think there's a different hurdle for putting language into a label and don't

think that label language should be based primarily on secondary exploratory analyses.

DR. HENDELES: Leslie Hendeles. I voted yes. I think the effect was small, but there was substantial evidence of that effect. I think the supporting evidence is the decrease in mortality and the improvement in lung function.

DR. HONSINGER: Richard Honsinger. I voted yes. Eight thousand patients, almost 8,000 patients, two studies of a six-month trial certainly showed the benefit. The four-year trial showed that this drug does not have tachyphylaxis and that it can be used long-term with benefit.

The study of the St. George questionnaire, I'm not surprised that it didn't turn out to meet the statistics that we would have liked. These are sick people. We try to make them better. We don't make them well.

DR. BRANTLY: Thank you very much.

I'd like to move on to discussion regarding -- let me just go back.

Is there any additional data that might

be useful for studies in the future or specifically around this particular issue? Any comment? Dr. Knoell?

DR. KNOELL: Just very briefly. We touched on it. We also identified it's very difficult to do, but continued pursuit of trying to look for inflammatory indices, whether there is a direct or indirect effect.

DR. BRANTLY: I would like to encourage the sponsor to look at in more detail about the exact mechanisms in which this occurs. I think it's important both for this particular drug, as well as the field in discovery. I think that while it's a compelling argument to talk about airway patency, it is not proven and it should be proven to the best of our ability.

Dr. Platts-Mills?

DR. PLATTS-MILLS: Apologies. I would like to encourage the company to continue looking at ways of -- almost along the same lines of what is the mechanism of exacerbations, how does this drug prevent them and, above all, how does

pulmonary rehab combined with bronchodilation in long-term improvement, using six-minute walking or some other measurement of improvement.

DR. BRANTLY: Dr. Schoenfeld?

DR. SCHOENFELD: I don't think we need any additional data. I want to commend the sponsor for doing a long-term study. I think long-term studies are extremely difficult to do and incredibly important for finding out the full spectrum of what a drug does. Every long-term disease should have a long-term study and I think it's great that this was done.

DR. BRANTLY: I'd like to now move on to question 4. Do the data from the Trial 205.235, the UPLIFT, adequately address the potential safety signal of stroke events and if not, what additional data is needed?

Discussion? Dr. Schoenfeld?

DR. SCHOENFELD: This is a difficult question. I'm going to answer yes on this, but the issue is what really are the standards for demonstrating safety. It's very difficult to

demonstrate safety, especially in regard to a rare event, to a really tight confidence interval and it sort of can't be done.

I think this is enough data to sort of obviate the previous concerns that were based on a lot less data. So we now know that the stroke risk isn't twofold and I think we know that from this study.

Whether there's a slight increased risk in stroke we can't tell and I think it throws it back to -- we're sort of thrown back to the surveillance that's going to have to go on in the future with many, many more patients. If it appears that there is an increased risk of anything, then, of course, it should be studied.

I think, also, a 30 percent increased risk of stroke, which is the top of the confidence interval, would be extremely difficult to rule out and, also, may not be that relevant in a disease with a mortality of 5 to, what was it, 10 to 15 percent a year. It may not be that relevant, a 30

percent increase in the risk of stroke.

DR. BRANTLY: Dr. Platts-Mills?

DR. PLATTS-MILLS: Can I ask the sponsor two questions? How closely was blood pressure monitored during this four-year period? Clearly, blood pressure is the major risk factor for stroke in this age group. So that's one question.

How many of the patients were taking low dose aspirin? Most men in the United States are taking low dose aspirin. Is that true internationally at this point and does that influence the risk of stroke or was any other drug they were taking influencing the risk of stroke?

DR. KESTEN: So two questions. One, Dr. Platts-Mills, is the blood pressure, hypertension, and the other is the aspirin. At clinic visits where we measured spirometry, vital signs were measured, heart rate and blood pressure. Then we looked at the proportion of patients who had what we considered a marked change or significant change.

Overall, whichever way we'd look at it,

we couldn't see treatment differences and we haven't seen treatment differences in blood pressure across trials. But those are single measurements at clinic visits. The other way, if I may, to look at it is through adverse event reporting.

DR. PLATTS-MILLS: But more seriously, what policy was laid down if blood pressure was found to be elevated in relation to treatment of blood pressure?

DR. KESTEN: There was no policy. We were expecting that treating physicians would treat their patients as they normally would. We certainly had no restrictions on that and, as I said, we tried to have this as a real world study.

We looked, also, at adverse event reporting of hypertension -- now, that will only give us the extremes when physicians are putting that down -- and didn't see any trends one way or the other. And I can't answer your question about aspirin specifically, how often it was and if there were any differences.

DR. PLATTS-MILLS: My question is designed to illustrate how extraordinarily difficult it would be to study 5,000 sick grownups over a four-year period.

DR. BRANTLY: Dr. Newman?

DR. NEWMAN: Somewhat along those same lines, a question that I have for the company on this. What do we know about the screen failures? If I remember right, in the UPLIFT study, we went into the study knowing that stroke was something of concern.

First of all, is that true or not? Was that something that the centers would have been aware of?

Why don't you answer that one first?

DR. KESTEN: No. Actually, when we started this, which was not quite 10 years ago, but it was a while ago, it was not an issue.

DR. NEWMAN: So not at any time during the course of this study.

DR. KESTEN: Let me clarify that. I'm sorry to interrupt. The stroke signal that we

reported did occur during the study. So what we did is we asked the DSMB to specifically look at that in their sessions and their recommendation was, obviously, continue the trial.

DR. BRANTLY: Are there any further questions regarding this particular issue before us?

Dr. Hendeles?

DR. HENDELES: I just want to make a comment. I don't understand how a drug could cause a stroke if it doesn't get to the brain. It's a quaternary ammonium compound. It has very low bioavailability and it would not cross the blood-brain barrier. So it's very hard for me to understand what the mechanism would be if it did do that.

DR. PLATTS-MILLS: It doesn't have to cross the blood-brain barrier.

DR. HENDELES: Then it wouldn't be a drug-induced stroke. In other words, what I'm talking about is a drug-induced stroke.

DR. BRANTLY: If we're going to speak,

speak on the microphone, please.

DR. SCHOENFELD: This isn't my field at all, but isn't it possible that the drug could cause clotting in the vasculature and then it would cause stroke later on? I suppose we could also ask if there were changes in pulmonary embolism, but that's pretty rare, as well, I guess.

DR. HENDELES: But none of those are an effect of an anticholinergic.

DR. BRANTLY: Dr. Newman?

DR. NEWMAN: I want to throw out a question to my colleagues here. This has to do with the point about generalizability of findings. If you design a study that excludes people who have recent prior MI, severe arrhythmias and heart failure, and we know that there is a covariance with stroke risk for people in those categories, can we really generalize more broadly about whether the studies that we have to rely on have ruled out stroke?

Basically, can we go out and say, more broadly, stroke is not a problem?

DR. BRANTLY: Dr. Schoenfeld?

DR. SCHOENFELD: I think one of the interesting questions is how safe does a drug have to be to be safe. So, therefore, in that case, we want to look at the absolute risk, not the relative risk.

So we've ruled out a relative risk of a 30 percent increase, because that's the top of the confidence interval. One could even say, well, should we really use the top of the confidence interval. If you're a Bayesian, you'll say we're ruling out a risk of 2.5 percent risk and maybe 70 percent sure would be good enough for me, which is one standard deviation, which then would be around a 20 percent increase in risk.

But the thing is, is the percent increase in risk that relevant? That is, does it matter to a patient whether they have a 1 percent chance of a stroke or a 1.2 percent chance of a stroke? It would seem to me that if I was balancing that against feeling better, I would do with the feeling better situation. So there is a question of how

safe and that question is very, very specific to the population.

So if we were talking about giving a drug to children, which -- well, even then, a 1.2 percent increase in their risk of stroke is very small, also. You have to look at this from the point of view o the population and from the point of view of the absolute risk. So it becomes a big judgment as to whether this is serious and how important this is. A twofold increase or a threefold increase is always, obviously, important.

DR. BRANTLY: Dr. Newman?

DR. NEWMAN: So if you could just follow that logic a little further for me, if you would. Think about a 65-year-old man or woman and the study that you're relying on to answer the question has potentially excluded people who are at risk for stroke, because you've excluded people who have cardiovascular disease, if this is the population that you want to treat to begin with.

DR. SCHOENFELD: I didn't believe that it did exclude those people, did it, the UPLIFT study?

DR. KESTEN: Thank you. For the UPLIFT study -- you are correct in what you say, but we had a number of people, a significant proportion with cardiovascular disease. What we sought to do is just at the time of randomization, not recruit unstable patients who would not be reasonably expected to complete the trial. This is four years and these patients do develop all sorts of co-morbidities that are diagnosed during the trial.

Just in terms of the frame of the question here, just as a clarification, we didn't expect and we don't know of a mechanism through direct muscarinic pharmacology and this was generated from information provided from Boehringer Ingelheim's safety database that led to the early communication.

The exact same analysis, the same safety database, except for a lot more patients, 162 versus low 40s, in fact, with perhaps more liberal inclusion criteria added to that, and that's the frame of the signal of stroke that was forwarded and that was a fourfold increase in the database.

DR. BRANTLY: Other comments?

DR. PLATTS-MILLS: Just to repeat. The idea of excluding cardiovascular risk in 65-year-old men who are already sick is ridiculous. They are clearly all at risk and, in this case, at very high risk of thrombotic and cardiovascular events.

DR. BRANTLY: If there's not any further discussion, I'd like to reread the question one more time and then we'll vote.

Do the data from the UPLIFT trial adequately address the potential safety signal of stroke events?

Can you vote now?

[Voting.]

DR. BRANTLY: Can we put the data up?

So voting results for question 4 are yes-11, no-1, abstain zero.

I'd like to begin with Dr. Honsinger explaining his vote.

DR. HONSINGER: I voted yes. To me, the UPLIFT trial looked at long-term in 5,000 patients. The other studies we looked at were not that

extensive. They did not study all the same drug. There were things other than tiotropium involved. They weren't as long a term of study. I think that we don't need to do any further studies for this suspicion.

DR. HENDELES: Leslie Hendeles. I voted yes. I think the data very clearly, from a randomized control trial that lasted as long as it did in as large a population as it was, from my view, excludes it, especially when I have the bias that if the drug doesn't get to the brain, other than causing blood effects, that it probably wouldn't be a drug-induced effect.

DR. HENNESSY: Sean Hennessy. I voted yes, because all of the relative risks are close to and below 1 and all of the confidence intervals exclude numbers that are even reasonably high risks.

MS. HOLKA: Andrea Holka. I voted yes. I don't believe that there was a clear stroke signal.

DR. TERRY: Peter Terry. I voted yes

based on the strength of the study design and the numbers and the length of time of follow-up.

DR. LESAR: Timothy Lesar. I voted yes, again, on the results of the UPLIFT trial.

DR. NEWMAN: Lee Newman. I'm the "no" guy and it's because I think that -- and I almost abstained, but I just think this is still a gray area. I don't actually know what study you could do to better address it, but I think it's still gray.

I am concerned about taking this message out to people more broadly to say it definitely does not cause stroke, because we haven't really done a study that matches the population of people who are going to be taking the drug.

To that point, I think having the opportunity to look at the post-marketing data and potentially being more informative, although it's going to be numerator data, I think, in some ways, that's where we ultimately will find out when people who do have higher cardiovascular risk and stroke risk are given this drug, unfortunately.

DR. BRANTLY: Mark Brantly. I voted yes,

because I believe the UPLIFT data does not support any evidence of a safety signal in the stroke.

DR. WOLFE: Sid Wolfe. I voted yes, because the question -- I am a strict stickler for questions -- is does it adequately address the safety signal. It does address it and, as has been pointed out, the upper bound is not that high.

With common events, such as strokes or heart attacks, it is I don't think that likely that we're going to learn anything more from post-marketing spontaneous adverse reports for things like liver damage and so forth. They are the gold standard. So I think that the data that there are now are comforting enough, from my perspective, that I voted yes.

DR. SCHOENFELD: I voted yes for the same reasons.

DR. PLATTS-MILLS: Tom Platts-Mills. I voted yes. I think it's important to say "adequately address." They adequately address the potential safety signal of stroke events. Excluding a stroke signal would be incredibly

difficult and I don't think it's a reasonable thing to ask for. I think the data in UPLIFT adequately addresses the potential safety signal and gives no suggestion that there is a such a signal.

DR. KNOELL: I voted yes for reasons already stated. Then to just simply comment on what we already talked about earlier, if this was Respimat, I'd obviously be concerned. I think as you expressed to us today, considering that that drug remains on the market, even at the 5 microgram indication, that you're going to continue to look into that drug and its potential toxicity profile.

DR. BRANTLY: I'd just like to go back for one moment and ask Dr. Newman to comment on what additional data he would require in this particular case.

DR. NEWMAN: I already answered that. I don't actually know that you could do the study that you could acquire the additional data. That's why, as I said, this is gray. I think it's going to remain gray.

DR. BRANTLY: Very good.

Let's go on to question number 5. Do the data from the UPLIFT trial adequately address the potential safety signal of adverse cardiovascular outcomes?

Let me begin with the discussion.

No comments? Very good.

Excuse me. Dr. Honsinger?

DR. HONSINGER: Certainly, if these people live longer and are more active, they may have more cardiovascular outcomes. If they should happen to be hospitalized more, they'll probably have more -- excuse me -- they'll have less. If they're hospitalized more, they'll probably have more cardiovascular outcomes. There are a lot of other variables that affect this other than taking the drug.

DR. PLATTS-MILLS: Dick, are you implying that if they have better lung function and they do more exercise, they'll have more accidents and, therefore, end up hurting themselves? That's quite likely.

DR. HONSINGER: Well, they all will have

cardiac events if they should live long enough.

DR. PLATTS-MILLS: I think the hope is, and I think something that the company could try and focus on is showing that improved lung function allows more activity and decreased cardiovascular events, and I think that would be a really interesting outcome.

DR. BRANTLY: Dr. Hendeles?

DR. HENDELES: Just to respond to Dr. Platts-Mills, I think their TV ads already do that.

DR. PLATTS-MILLS: It's much more interesting than that, because the latest computer game, Wii, has now got an aerobic element to it. Have you seen this thing? There's a paper that's just been published in the cardiovascular literature showing that playing -- it's a Nintendo game called Wii and that it actually has aerobic effects.

I think Boehringer Ingelheim should be encouraged to combine with Nintendo.

[Laughter.]

DR. BRANTLY: I'm sorry. That has to

come to a different committee because of the device issue there.

[Laughter.]

DR. BRANTLY: With this, let's go ahead and vote.

[Voting.]

DR. BRANTLY: Can we show the data?

The results for question 5 are yes-11, no-zero and 1 abstaining.

I'd like to begin with Dr. Knoell.

DR. KNOELL: I voted yes and it's for the same reasons we just discussed with the last issue. I saw unequivocally no indices to put me at concern for increased cardiovascular risk with continued use of this medication.

DR. PLATTS-MILLS: Dr. Platts-Mills. I voted yes, because I think the data in the UPLIFT are convincing and the overall mortality data is convincing. I think the data adequately addresses the potential safety signal.

DR. SCHOENFELD: I found the UPLIFT data convincing.

DR. WOLFE: I voted yes. But again, if the question had to do with the other dosage form, which looks like it gets absorbed more at higher blood levels, it would be different. But we're confining it to UPLIFT, so that's why I voted yes.

DR. BRANTLY: Mark Brantly. I voted yes. I believe the data is compelling that there is no increased cardiovascular risk.

DR. NEWMAN: Lee Newman. This time, I abstained, because resistance is futile. But rather than voting yes, I still want to make the point that I worry about the generalizability. If it was a specific question, it might have been yes, but I worry about the generalizability from this one study to what we tell the populous.

DR. LESAR: Timothy Lesar. I voted yes. Again, I thought it was adequately shown by the UPLIFT data.

DR. TERRY: Peter Terry. I voted yes based on the strength of the UPLIFT data, but also on the weakness of the studies that indicated that the safety signal should be raised.

MS. HOLKA: Andrea Holka. I voted yes based on UPLIFT not suggesting an increase in rates of cardiovascular events.

DR. HENNESSY: Sean Hennessy. I voted yes for reasons already discussed.

DR. HENDELES: Leslie Hendeles. I voted yes for those reasons and for the fact that there was even a suggestion that it may have helped cardiovascular outcomes.

DR. HONSINGER: Richard Honsinger. I voted yes, the strength of the UPLIFT data and the weakness of the alternative data.

DR. BRANTLY: Well, I think that our meeting has come to a conclusion. I'd like to thank the committee for taking the time to consider this and would like to also thank both the FDA, as well as the sponsor for providing us with some opportunity to discuss this issue.

DR. ROSEBRAUGH: I would also like to take the opportunity to thank the committee. We really appreciate the thoughtfulness with your discussion. I think we learned a lot from this.

I've always told Dr. Chowdhury I consider it a successful meeting if I don't have to say anything, and then he had to go and leave. So his performance evaluation will reflect that.

[Laughter.]

DR. ROSEBRAUGH: But otherwise, I'd like to thank you guys again. We really appreciate it.

[Whereupon, at 3:08 p.m., the meeting was concluded.]